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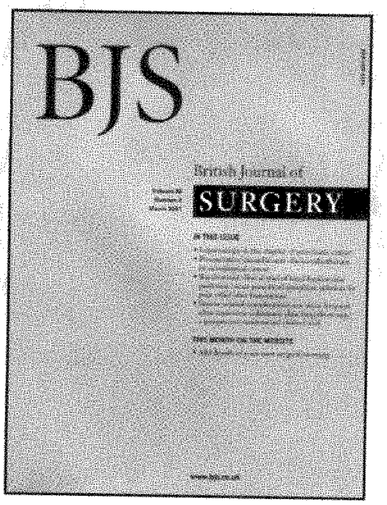

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Ethics of surgical innovation

G. Gillett

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Clinical surgery typically aims to correct an abnormality producing an illness. The risks and varying benefits that result create an ethical imperative to try to improve surgical practice by research and innovation. Most operations are intellectually fairly simple. Surgeons remove lumps, relieve stenoses, alleviate pressure compromising function or causing pain, and eradicate infection. Sometimes the corrective intervention is so obvious in its effect that there is no uncertainty about its worth, for instance removing a subdural haematoma causing pressure on the brain, resecting a tumour obstructing the bowel, treating a septicaemia, or unblocking an artery. In such cases the clinician can see that he or she has done what was needed. However, in other cases, while the immediate effect is accepted as good treatment, the overall or long-term efficacy is less clear; carotid endarterectomy is an example. What is more, some surgical techniques are supported by theories that are subject to criticism, such as gastric ulcer surgery and radical mastectomy. In such circumstances trials must be done. Finally, some surgical innovations are technical improvements on accepted treatments.

If an innovation is more than a technical improvement on an existing technique it may be regarded as a new approach to a problem. In such circumstances one can identify two possible situations. First, the aim of the operation in terms of correction of abnormal structure is itself well proven to be effective in treating the disease, for instance removal of a life-threatening tumour of the brain. Second, the aim of the operation has never itself been well proven but is a matter of accepted practice. In both cases the new technique should be compared with best current treatment. In the second situation it is evident that the currently accepted treatment should also be validated against no intervention at all to determine whether that treatment is advantageous to the sufferer of the disease or merely a sop to clinical activism.

It is useful to compare the assessment of surgery using clinical trials to the phases of introduction of drug treatments. Phase I studies of drugs are comparable to investigations of safety in surgery; surgeons do not operate on healthy volunteers and so must show that no harm is done by an innovation in suitable patients. Some ancillary investigations, such as mechanical testing or testing *in vitro*, may be needed before this stage. Phase II studies of drugs are related to efficacy in a clinical situation and, because the interventions used in surgery are often introduced because they appeal to the 'educated eye', a phase II equivalent may not be reached. Surgeons do not often ask whether correcting an obvious anomaly actually helps the patient. Surgical techniques, therefore, can move from safety testing direct to widespread clinical use on the basis of little more than intuition. This is far from satisfactory: a number of questions that ought to be asked when surgical innovation is being undertaken can be identified.

Is this operation a modification of an existing and widely accepted treatment or an alternative to such a treatment? There has often been a gradual shift in operative technique for a given problem, such that it is a question of degree as to when a modification becomes an innovation. A surgeon might do an operation in a certain way and believe that it is superior in technical terms to standard practice, but have neither good evidence that the standard practice is clearly beneficial nor, by implication, that the modification is a genuine improvement.

Why was this modification introduced? There are a number of reasons related to safety or ease of performing a procedure that lead to modifications. Some of these become accepted as reasons why the new method is better without any adequate testing as to whether, in fact, it is. One must ask whether a modification is likely to introduce significant new risks and answer that question by careful monitoring of cases in which it is used.

Should a prospective randomized double-blind controlled trial be done? Such a trial requires the investigator to be in a state of equipoise. Equipoise means that the investigator has no valid reason to believe that using one or other of two treatments will confer any advantage. In surgery, however, disturbances of equipoise may be based not only on clinical outcome but on factors proximate to the surgery (pain, time of operation, worries based on the 'educated eye'). Because of this it has been suggested that something like the principle of uncertainty might be a better way to go for surgeons[1]. This allows the doctor to reflect on the standard of evidence he or she has for the beliefs held and, where the evidence is inconclusive, to participate in a well designed trial to address the uncertainty. The difficulties with randomized and blinded trials of surgical techniques are well known. First, the surgeon has usually introduced the modification or new technique for a good set of reasons so that he or she is not in a state of equipoise, unless that equipoise is narrowly interpreted according to outcome alone. Second, given surgeons' individual preferences, the best comparisons that can often be achieved are prospective contemporaneous trials that involve the non-random allocation of patients to different treatments, or comparisons between retrospective series. Both of these present problems in that they fail to control for the differing skills of different surgeons, and they may not achieve comparability on other measures such as case-mix and perioperative management. Finally, the concept of blinding and placebo control may not be appropriate in surgery because placebo operations are not usually considered ethically acceptable, although this can be debated[2].

Has the patient been told that this is an innovation and offered alternative treatment? This is the single most important ethical consideration. Given that evidence about the efficacy of existing treatments might be poor by epidemiological standards, all that one can ask is that the new method should seem to be at least as good as, and no worse than, conventional treatment. The patient should be told of the options and how the advice that is being given relates to mainstream medical opinion. Many clinicians, and surgeons in particular, are bad at this; they do not inform the patient about uncertainties or options for treatment by other means. In the end, the patient must be empowered to make his or her own decision when clinical facts do not point unequivocally to a single mode of treatment; mastectomy or lumpectomy for breast cancer is an example. If this is done the patient becomes a participant in designing the treatment regimen and in monitoring the outcomes. Such partnerships allow medical innovation to proceed in a fruitful way because patients feel permitted to contribute their own observations, no matter how odd or unusual these seem to be.

In conclusion, innovation is necessary in surgery and so good research is also necessary to check on the effects. Surgeons and patients must enter these trials in a spirit of open and informed partnership, in which the patient is regarded as a coinvestigator. When significant innovation is in the offing, an independent ethical review should oversee the trials required to develop and test that innovation. Despite all of this there remain reasons why one should not unnecessarily obstruct surgical innovation by always insisting on orthodox and rigid adherence to the tenets of the prospective randomized double-blind controlled trial. This is especially so when an 'educated eye' might inform us that a procedural variation is more technically useful than an existing operative technique.

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Leading article

Medical negligence and the law

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They call us 'ambulance chasers' and accuse us of inspiring defensive medicine. However, the truth is that lawyers do not determine what is or is not clinical negligence. That is the domain of other medical/surgical experts in the same specialism as that in which the 'mistake' occurred. In my experience the doctor's best friend is, in fact, the specialist lawyer who prevents frivolous and unwarranted claims from ever starting. However, what is undoubtedly a problem for surgeons – just as it is for lawyers – is determining what exactly is or is not clinical negligence. Who defines it and how should the definition be interpreted? Just what is the required standard of treatment?

A lawyer – especially an academic lawyer – might tell you that negligence arises when one person owes to another a duty of care (and there is no doubt that a doctor owes a duty of care to his or her patients), breaches that duty, and reasonably foreseeable harm (measurable in money damages) flows from that breach. The basic judicial definition in English law – and all jurisdictions based on English common law – might be stated as 'negligence is the omission to do something which a reasonable man, guided upon those considerations which ordinarily regulate the conduct of human affairs, would do, or doing something which a prudent and reasonable man would not do'[1].

But the real question is 'Who is the reasonable man?' Sometimes he is the ordinary man, the average man, or 'the man on the Clapham Omnibus'[2], but not always. The standard of care in a situation requiring the exercise of special skill or competence (e.g. in medicine) is not judged by the ordinary man on the bus but by the standards of appropriate peers (the doctor on the Clapham Omnibus perhaps). The classic statement of the test of negligence in medicine is what has come to be known as the 'Bolam test'[3], negligence being said to be 'failure to act in accordance with the standards of reasonably competent medical men at the time'. However, the judge in that case went on to provide what is known as the 'Bolam defence', the scourge of clinical negligence lawyers and the saviour of many medical practitioners: 'A doctor is not negligent if he is acting in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art merely because there is a body of such opinion that takes a contrary view'.

The situation in Scotland is similarly defined in Hunter *versus* Hanley[4], which states that 'the course the doctor adopted' must be 'one which no professional man of ordinary skill would have taken if he had been acting with ordinary care'. This slight variation on Bolam (albeit predating it) is echoed in the more recent English case of Bolitho[5] which confirmed the principles in Bolam but made it clear that the 'practice accepted as proper by a responsible body of medical men skilled in that particular art' must also be reasonable, i.e. capable of withstanding logical analysis.

Even though it is more that 200 years since the USA was an English common law jurisdiction, just as in most British Commonwealth countries the same basic principles (but not precisely the same exact definitions) remain there. Thus in the USA a doctor must possess and exercise the knowledge and skill of a member of his or her profession in good standing in the same or similar communities. He or she is also expected to use such superior judgement, skill and knowledge as is actually possessed, i.e. the standard for a neurosurgeon is that of a reasonable neurosurgeon in the same or a similar community.

It seems, therefore, that the level of skill required in all three of these jurisdictions is that of the reasonable practitioner in the particular field of practice of the doctor in question. However, the way in which this is interpreted very much depends on who is charged with the interpretation. In many jurisdictions, such as England, it will be a judge sitting alone and using his professional skill to apply the test to the evidence presented by an independent expert in the relevant specialism. In jury-based systems, however, such as in the USA, while the same or a similar test applies, it is being applied by jurors who undoubtedly see themselves as patients. Their deliberations are steered by the principle of 'there but for the grace of God go I'. The judge will apply the reasonable doctor test – from the position perhaps of the reasonable judge on the Clapham Omnibus – but the juror almost certainly (albeit wrongly) will apply the test of the reasonable patient on the same bus or on the New York Metro. The former, coupled with Bolam, will protect against defensive medicine, but the latter may well cause it, especially when those same jurors set the damages at a level they would wish to receive if they were the injured patient.

However, the proper definitions seem fairly clear despite the trappings of judicial language and legal-speak. What English academic lawyers are now contemplating is the impact on these definitions of the European Convention on Human Rights which became embodied in English law in

October 2000[6]. A number of European jurisdictions have been dealing with this Convention for some time and it has been law in Scotland since May 1999. While it is fair to say that most cases brought under the Scottish Act have failed, the impact in England could be enormous as far as clinical negligence cases are concerned.

Article 2 of the Convention is entitled 'Right to Life'. However, its influence is not confined to a loss of life but encompasses any case in which injury has been sustained and a possible consequence of the conduct complained of could have been a loss of life. In cases in which a public body is involved, including all National Health Service treatment by doctors in UK public hospitals (but not private medicine in private hospitals), the implication of this article is that Bolam could be challenged in the English courts and overruled. In a case under this article in the European Court before the implementation of the 1998 Human Rights Act[7] it was determined that the state must take 'adequate and appropriate steps' to protect life. Unless the requirement to provide 'adequate medical care' is the same as taking 'reasonable care', which it almost certainly is not, then arguably Bolam is defunct. It may also be argued that if the provision were adequate there would not have been an adverse outcome. So there may be no need to prove negligence at all, merely an adverse (or less than planned for) outcome: surely no-fault compensation by another name? Only time and the English courts will tell.

In practice, therefore, the situation is as I have already stated, namely that negligence can only be proved by another medical man in that field 'skilled in that particular art' in accordance with Bolam. It cannot be proved by lawyers who, while they set out the definitions discussed above, can only apply those definitions to evidence given by medical witnesses from the particular specialty in question. Subject to what effects the Human Rights Act might in future have in England, perhaps for the present the test as to whether you have been negligent should be for you to ask yourself the question, because only you (and your peers) can properly answer it. Lawyers certainly cannot, although we would like to think we can.

References

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Systematic review and meta-analysis of emergency ultrasonography for blunt abdominal trauma

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Background: How precise and reliable is ultrasonography as a primary tool for injury assessment in blunt abdominal trauma?

Methods: A systematic review and meta-analysis were conducted of prospective clinical trials of ultrasonography for blunt abdominal trauma. Publications were retrieved by structured searching among databases, review articles and major text books. Authors and experts in the field were contacted for original and unpublished data. For statistical analysis, summary receiver operating characteristic curves (SROCs) were computed using weighted and robust regression models, with Q* denoting the shoulder of the curve. Post-test probabilities were calculated as a function of pooled likelihood ratios (LRs).

Results: Thirty of 123 trials enrolling 9047 patients were eligible for final analysis. With respect to targeting organ lesions, ultrasonography showed a summary Q* value of 0·91 (inverse variance weights, 95 per cent confidence interval (c.i.) 0·76–1·07); negative predictive values ranged from 0·72 to 0·99. A similar SROC slope was calculated for screening for free fluid (Q* = 0·89 (95 per cent c.i. 0·73–1·05)). Ultrasonography detects the presence of organ lesions, but fails to exclude abdominal injuries (random effects negative LR 0·23 (95 per cent c.i. 0·18–0·28)). Given a pretest probability of 50 per cent for blunt abdominal injury, a post-test probability of nearly 25 per cent remains in the case of a negative sonogram.

Conclusion: Despite its high specificity, ultrasonography has an unexpectedly low sensitivity for the detection of both free fluid and organ lesions. In clinically suspected abdominal trauma, another assessment (e.g. helical computed tomography) must be performed regardless of the initial ultrasonographic findings.

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Introduction

Ultrasonography is widely used in the initial diagnostic assessment of blunt abdominal trauma. In the emergency setting, the examination in four standard planes (focused assessment with sonography for trauma, FAST) aims to detect or to exclude free intraperitoneal fluid, indicating organ lacerations. The spleen and liver are most frequently affected by blunt forces, with incidences of injury varying between 20 and 60 per cent[1–5]. Modern ultrasound equipment enables the detection of fluid collections as small as 10–15 ml close to lacerated viscera[6]. A major concern remains, however, about the reliability of peritoneal effusion as a surrogate marker of organ injury. According to recent reports, the frequency of visceral lesions not accompanied by free fluid ranges from 10 to 30 per cent[7–9].

The usefulness of a diagnostic test derives from three important clinical questions: (1) Is this tool precise and available at reasonable cost? (2) Can the pretest probability

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The Editors have satisfied themselves that all authors have contributed significantly to this publication of the target disorder in any patient be reasonably estimated? (3) Will the post-test probability achieved by application of the diagnostic test change the therapeutic action? The pretest probability (or prevalence) equates to the likelihood of the presence of a disease that can be gained by clinical judgement and expertise alone. If the diagnosis seems clinically obvious, the ability of a test to confirm it is not helpful (although its ability to exclude the diagnosis might be of value). Intra-abdominal injuries are difficult to assess clinically and so the FAST examination provides an excellent example of a test worthy of critical appraisal in this era of evidence-based medicine.

An abundance of articles on ultrasonography for abdominal trauma is available but no systematic review has yet been published to establish its diagnostic value compared with other investigative modalities (such as clinical monitoring, peritoneal lavage, laparotomy and computed tomography (CT)). The authors reasoned that a meta-analysis should highlight the strengths and weaknesses of emergency ultrasonography as a primary tool in the assessment of the injury pattern in blunt abdominal trauma. Such an analysis may provide good evidence for the development of clinical practice guidelines.

Method

The project started with a question – in a patient with suspected blunt abdominal trauma, does a negative sonogram indicate a need for further diagnostic evaluation to exclude organ injury?

Prospective clinical trials beginning with the first available reference on diagnostic ultrasonography up to July 2000 were eligible for inclusion in the analysis. In line with validated retrieval strategies[10] the major medical databases (i.e. Medline, Embase and the Cochrane Library of Systematic Reviews) were searched for studies using the following subject headings: ultrasound, ultrasonography, FAST, free fluid, haemoperitoneum, organ, lesion, laceration, rupture, trauma, parenchyma, injury, blunt, abdominal, prospective, clinical trial, review and meta-analysis. Searching terms were alternately connected by Boolean operators. The homepage of the German National Library of Medicine (Cologne, Germany) and web-links provided by the National Institute of Health (Bethesda, Maryland, USA) were reviewed for further data sources. No restrictions were made with respect to language. In a second retrieval phase, references in the original papers were examined for other publications fitting the above terms and these related articles were accessed. This procedure was repeated in a further two phases. An extensive manual search was also performed among publications and text books on the diagnosis and treatment of abdominal injuries[11–25]. Authors and other experts were contacted to request information on original and unpublished data but this did not lead to additional information.

In general, quality criteria differ among diagnostic and therapeutic studies. Randomization is a recognized prerequisite to balance confounding variables between treatment arms in a therapeutic trial. However, a trial of a diagnostic test requires an independent and blinded comparison with a reference standard rather than randomization[26]. Although blinding appears to be basically possible for ultrasonography, the blinded evaluation of hard copy sonograms does not always allow the dynamic properties of this technique to be appreciated; video documentation is desirable but probably unrealistic in this context. It was decided therefore that non-blinded comparisons should be clinically acceptable.

Each trial was rated qualitatively and by two authors (D.S., K.B.) with respect to two main features: (1) Were patients enrolled consecutively in the trial? (2) Was a reference standard (i.e. CT, surgery, peritoneal lavage, clinical observation) applied independently and regardless of the results of ultrasonography in any case?

Quality grading followed the recommendations of the NHS Research and Development Centre for Evidence-Based Medicine, Oxford, UK[26], with the most common levels of evidence defined as IIb (independent blind comparison but either in non-consecutive patients or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard) and IIIb (independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients). Reference standards that allowed a comparison and summary of trial results were used. Endpoints had to have been stated in more than one trial. Studies were evaluated separately for the detection of free fluid and the recognition of organ injury. A sensitivity analysis was carried out to assess the performance of ultrasonography for different clinical conditions (i.e. screening for solid and hollow organ injuries, grade of examiner's experience, paediatric trauma, haemodynamic instability).

Statistical analysis

Statistics included sensitivity, specificity and accuracy of emergency ultrasonography compared with the reference standard. The accuracy of a diagnostic test is derived from the sum of all true-positive and true-negative findings divided by the study size. Weighted negative predictive values (NPVs) were regressed to the prevalence of either organ injury or free fluid as given in individual studies. Related 95 per cent confidence intervals (c.i.) were computed as a function of the standard error[27–30]. All two-by-two tables were adjusted for continuity. As a global measure of test performance, areas under the receiver operating characteristic (ROC) curves were estimated for individual trials. In general, ROC curves indicate the trade-off between true-positive rates (TPR, or sensitivity) and false-positive rates (FPR, or 1 – specificity) for various thresholds.

The common effect size was estimated using summary ROC (SROC) curves as proposed by Moses *et al.*[31,32]. With β_0 denoting the intercept and β_i the slope of the regression line, the common log odds ratio, $D = \beta_0 + \beta_i S$, was fitted using both a robust regression method as well as the inverse variance weights of S, a variable derived from the logistic transformation of TPR and FPR. On the assumption that high sensitivity at the cost of low specificity is beyond clinical relevance, this model discards much of the area under the SROC curve. As another common indicator of test efficacy, the intersection of the pooled ROC curve with the line where sensitivity equals specificity was computed as

$$Q^* = \frac{1}{(1 + e^{-\beta_0/2})}.$$

To obtain probabilities for the presence of abdominal injury given an individual prevalence, likelihood ratios (LRs) for positive and negative test results were calculated as the ratio of the post-test and the pretest odds. Fixed effects pooling was realized by a modified Mantel–Haenszel model[27,29]. Heterogeneity between trials was calculated by χ^2 statistics for $k - 1$ degrees of freedom. Where there was significant heterogeneity, a random effects model, as described by DerSimonian and Laird, was computed to summarize trial results[28]. This model claims a more relaxed common study effect, and trials are regarded as random samples of all investigations available in the present and the future. The weight of each study is calculated as

$$W'iDL = \frac{1}{(se(\hat{\Theta}\,i)^2 + \hat{\tau}^2)}$$

where $se(\hat{\Theta}\,i)$ is the standard error of logLR and $\hat{\tau}^2$ represents the random effects estimator.

A multivariate linear regression analysis was performed to assess a possible stage migration effect (Will Rogers phenomenon). The hypothesis was that an improvement in imaging quality might have influenced the diagnostic accuracy achieved by emergency ultrasonography over the past two decades since the introduction of this technique.

All biostatistical models were programmed in Excel 8.0 for Windows (Microsoft Corporation, Redmond, Washington, USA). Critical χ^2 values and individual areas under the ROC curves with 95 per cent c.i. derived from Hanley's standard error were obtained from Stata 6.0 (Stata Corporation, College Station, Texas, USA). Two-tailed $P < 0.05$ was considered statistically significant.

Results

Exploring the medical databases, over 300 publications were found by the structured search strategy. By reviewing either the title or the abstract, 123 citations were considered promising for further evaluation. All relevant original papers were reviewed thoroughly, uncovering a majority of retrospective studies, case reports and case series. This left 30 trials containing data on 9047 patients for further analysis. None of these 30 studies provided a Ib level of evidence and so it was decided to work on investigations corresponding to a grade B recommendation (i.e. studies of IIb and IIIb level of evidence). A complete list of all

Table 1 Characteristics of included studies investigating the diagnostic value of emergency ultrasonography for the detection of organ injury

Reference	Year	Diagnostic gold standard	Level of evidence	Enrolment	Blinding	Prevalence	TP	FN	TN	FP
Akgür *et al.*[2]	1997	Laparotomy, CT, observation	II b	Consecutive	No	0·24	42	8	157	1
Froelich *et al.*[77]	1982	^{99m}Tc scintigraphy	II b	Consecutive	Evaluator	0·58	13	2	10	1
Förster *et al.*[33]	1992	Laparotomy, DPL, CT	III b	Consecutive	No	0·21	28	1	107	4
Goletti *et al.*[34]	1994	Laparotomy, DPL, CT, observation	III b	Consecutive	No	0·41	26	4	42	1
Healey *et al.*[64]	1996	Laparotomy, DPL, CT, observation	II b	Consecutive	No	0·06	45	6	728	17
Katz *et al.*[55]	1996	CT, observation	II b	Consecutive	No	0·09	10	1	92	18
Krupnick *et al.*[41]	1997	CT*	III b	Case–control	Evaluator	0·50	20	12	32	0
McGahan *et al.*[35]	1997	Laparotomy, DPL, CT	III b	Non-consecutive	No	0·31	24	14	79	4
McKenney *et al.*[78]	1998	Laparotomy, DPL, CT, observation	II b	Consecutive	No	0·12	95	15	768	6
Röthlin *et al.*[36]	1993	Laparotomy, CT, observation	III b	Consecutive	No	0·18	24	31	257	1
Singh *et al.*[54]	1997	DPL, observation	II b	Consecutive	No	0·48	26	9	33	5

*Initial computed tomography (CT); ultrasonography after mean(s.d.) 5·5(1·0) days. TP, true positives; FN, false negatives; TN, true negatives; FP, false positives; DPL, diagnostic peritoneal lavage

Table 2 Characteristics of included studies investigating the diagnostic value of emergency ultrasonography for the detection of free fluid

Reference	Year	Diagnostic gold standard	Level of evidence	Enrolment	Blinding	Prevalence	TP	FN	TN	FP
Ballard *et al.*[37]	1999	Laparotomy, DPL, CT	III b	Non-consecutive	No	0·19	5	14	83	0
Boulanger *et al.*[42]	1996	DPL, CT	II b	Non-consecutive	No	0·16	51	12	326	11
Chiu *et al.*[7]	1997	Laparotomy, DPL, CT, observation	III b	Non-consecutive	No	0·07	37	15	720	0
Coley *et al.*[84]	2000	CT	II b	Consecutive	No	0·30	12	20	73	2
Hoffmann *et al.*[47]	1992	Laparotomy, DPL	II b	Consecutive	No	0·38	99	12	174	6
Ingeman *et al.*[43]	1996	Laparotomy, DPL, CT, observation	II b	Non-consecutive	Evaluator	0·25	18	6	70	3
Kern *et al.*[63]	1997	Laparotomy, DPL, CT, observation	II b	Consecutive	No	0·06	22	8	476	12
Liu *et al.*[53]	1993	Laparotomy, DPL, CT, observation	II b	Consecutive	No	0·65	33	3	18	1
McElveen *et al.*[38]	1997	Laparotomy, DPL, CT	III b	Non-consecutive	No	0·20	14	2	65	1
McKenney *et al.*[46]	1994	Laparotomy, DPL, CT	II b	Non-consecutive	No	0·18	29	6	164	1
McKenney *et al.*[39]	1996	Laparotomy, DPL, CT	III b	Non-consecutive	No	0·15	132	18	838	8
Rozycki *et al.*[79]	1993	Laparotomy, DPL, CT, observation	II b	Consecutive	No	0·19	71	19	369	17
Rozycki *et al.*[51]	1995	Laparotomy, DPL, CT, observation	II b	Consecutive	No	0·16	53	6	305	1
Rozycki *et al.*[56]	1998	Laparotomy, DPL, CT, observation	II b	Consecutive	No	0·06	58	16	1151	2
Shackford *et al.*[65]	1999	Laparotomy, DPL, CT, observation	II b	Consecutive	No	0·22	35	16	180	3
Thomas *et al.*[80]	1997	Laparotomy, DPL, CT, observation	II b	Consecutive	No	0·07	17	4	277	2
Tso *et al.*[45]	1992	Laparotomy, DPL, CT	II b	Non-consecutive	No	0·10	11	5	146	1
Wherrett *et al.*[44]	1996	DPL, CT	II b	Non-consecutive	Evaluator	0·29	17	3	44	5
Yeo A *et al.*[40]	1999	Laparotomy, DPL, CT, observation	III b	Non-consecutive	No	0·16	4	2	31	1

TP, true positives; FN, false negatives; TN, true negatives; FP, false positives; CT, computed tomography; DPL, diagnostic peritoneal lavage

publications is available from the authors on request. Characteristics and quality criteria of included studies are presented in *Tables 1* and *2*.

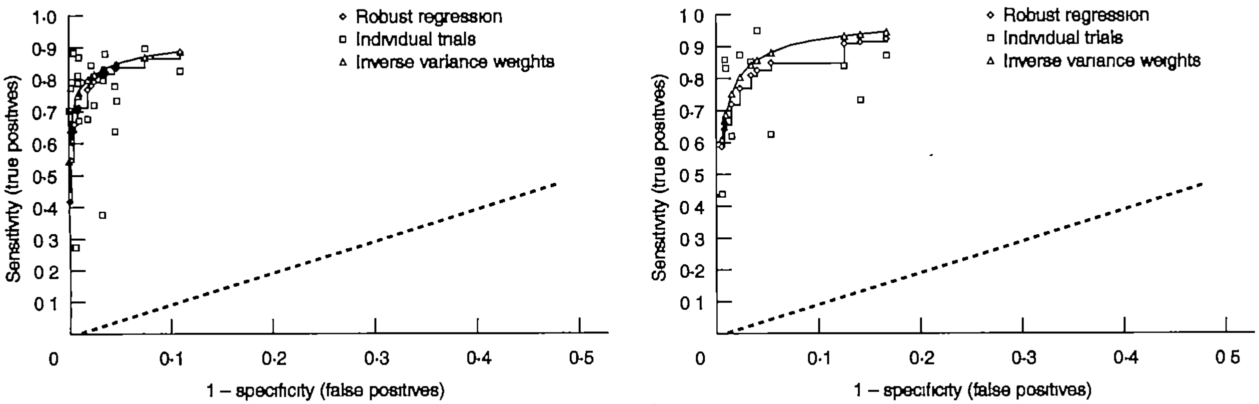
Nine trials lacked an independent comparison of the ultrasonography findings with the reference standard, fulfilling only IIIb criteria[7,33–40]. A further otherwise well designed case–control study also fitted this category[41]. Five level IIb and six level IIIb studies did not have consecutive enrolment of patients. This was due to lack of availability of a medical sonographer 24 h a day[85,42–44], or exclusive performance of emergency ultrasonography by only certain authors[38,40], or inclusion criteria focusing on a subset of patients or other 'convenience' sampling[7,37,39,45,46]. At least two dual publications of identical data in German and American journals were identified; some additional information was gained from subtle comparison of tables in the individual manuscripts[36,47–49]. Data from a subset of patients enrolled in a larger trial were published twice[46,50].

Recognition of organ injury

Eleven trials (six level IIb and five level IIIb studies) containing a total of 2819 patients evaluated the capability of ultrasonography to recognize organ lacerations. Individual studies allowed for a discrimination between pattern of injury (i.e. parenchymal or hollow organs); few data were available for summary statistics. The intersection Q^* was estimated as 0·91 (95 per cent c.i. 0·76–1·07) using inverse variance weights and 0·90 (95 per cent c.i. 0·75–1·05) using robust regression. The SROC curve is delineated in *Fig. 1a*. NPVs ranged from 0·72 to 0·99 (*Table 3* and *Fig. 2a*). Heterogeneity was substantial among trials concerning organ injury (χ^2 = 74·63 for positive LR and χ^2 = 57·05 for negative LR; P < 0·001). Random effects modelling resulted in a positive LR of 21·99 (95 per cent c.i. 15·08–32·06) and a negative LR of 0·23 (95 per cent c.i. 0·18–0·28). The related post-test probabilities are shown in *Fig. 3a*.

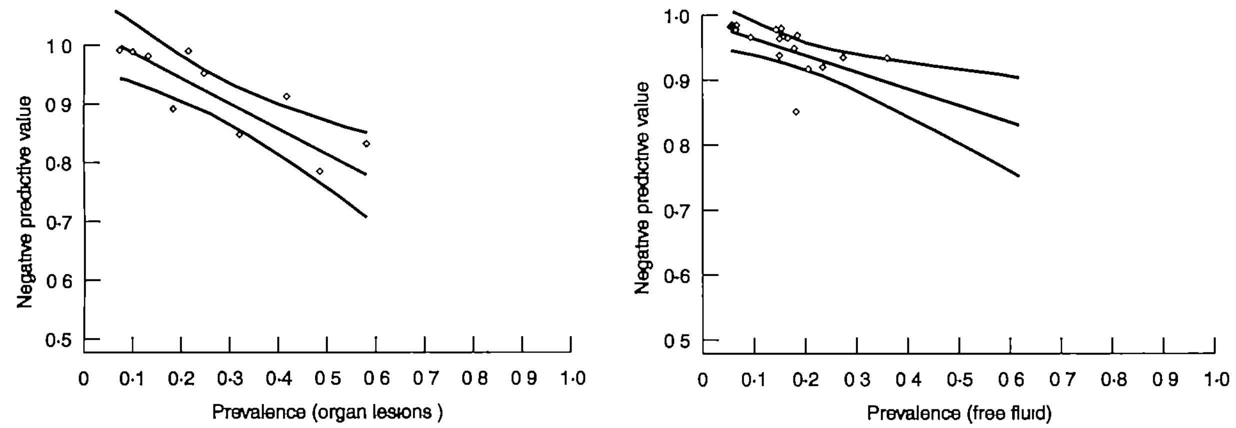
Detection of free intraperitoneal fluid

Nineteen publications containing data on 6492 patients could be analysed with regard to the detection of free intra-abdominal fluid. There were 14 studies providing a IIb level of evidence, and five more trials fulfilling level IIIb criteria. NPVs ranged from 0·78 to 0·99 (*Table 4* and *Fig. 2b*). The SROC curve derived from both regression models shoulders up to 0·89 (*Fig. 1b*). Confidence intervals ranged from 0·73 to 1·05 for weighted regression and from 0·76 to 1·03 for robust regression. Once again, significant heterogeneity was found among trials with critical χ^2 values of 64·91 and 124·64 for positive and negative LRs (P < 0·001). Random effects pooling led to a positive LR of 36·28 (95 per cent c.i. 28·97–45·44) and a negative LR of 0·24 (95 per cent c.i. 0·20–0·28) for this primary endpoint. The related probabilities are represented in *Fig. 3b*. Therefore, ultra-



a Organ injury **b** Free fluid

Fig. 1 Summary receiver operating characteristic curves for **a** organ lesions and **b** free fluid obtained from robust and weighted regression analysis of outcome measures derived from all included trials. The dotted line represents the theoretical plot of a test with no discrimination



a Organ injury **b** Free fluid

Fig. 2 Weighted negative predictive values with related 95 per cent confidence intervals as a function of prevalence for **a** organ lesions and **b** free fluid. Linear regression analysis adjusted for sample size

sonography appears to lead to similar changes from the pretest probability for both organ injury and haemoperitoneum.

Sensitivity analysis

Röthlin and colleagues[36,49] failed to prove differences in the diagnostic accuracy of ultrasonography in detecting lesions of particular organs. Eight of 22 splenic injuries could be visualized. Lesions of the liver and kidney were recognized in one of nine and two of ten cases respectively; one of three small bowel lacerations was detected by sonography. When targeting free fluid and organ lacerations, neither accuracy nor NPV differed between beginners and experienced sonographers. Results are summarized in *Table 5*. While other trials described injury patterns by means of proportions, no two-by-two tables could be calculated from the available data. The frequency of splenic lacerations exceeded 50 per cent in most studies[2,34,51–53].

Data were pooled from four trials investigating a paediatric population, yielding 501 patients[2,9,54,55]. Subset analysis did not allow a distinction between recognition of free fluid and organ injury. The related SROC curve is depicted in *Fig. 4a*. The summary measure Q* was estimated as 0·88 (95 per cent c.i. 0·33–1·42) using inverse variance weights and 0·87 (95 per cent c.i. 0·76–0·99) derived from robust regression. NPVs ranged from 0·72 to 0·98, with a prevalence of blunt abdominal injury ranging from 0·10 to 0·94. Results of emergency ultrasonography in children were similar to those of adult patients in cases of

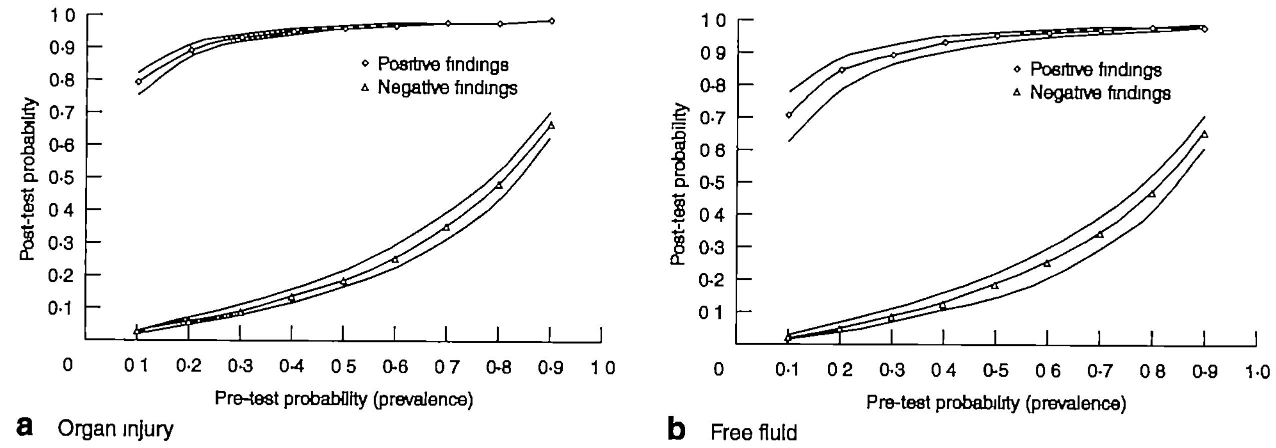


Fig. 3 Probability nomograms with 95 per cent confidence intervals derived from pooled likelihood ratios with random-effects modelling for a organ lesions and b free fluid. Post-test probabilities with related 95 per cent confidence intervals can be obtained for an individual preference

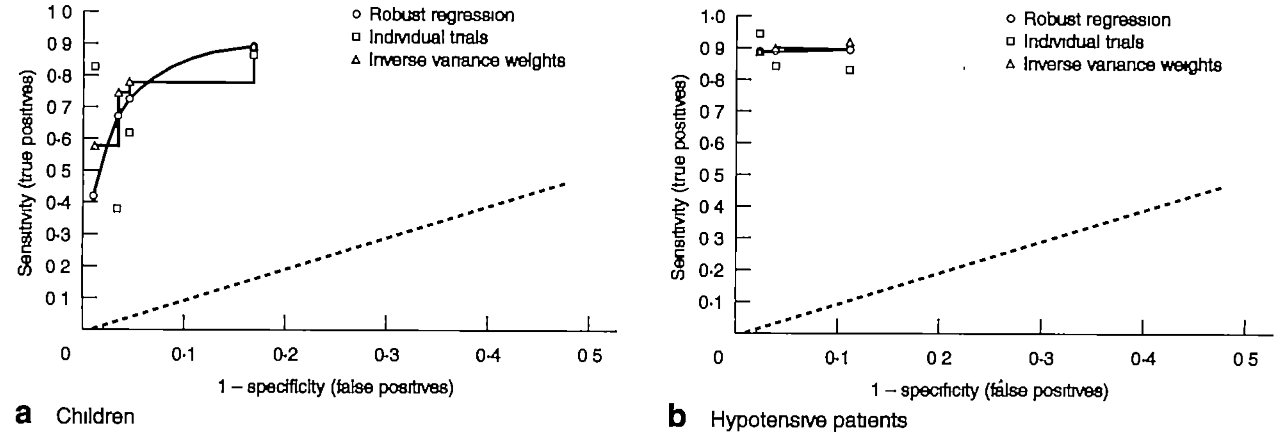


Fig. 4 Summary receiver operating characteristic curves obtained from robust and weighted regression analysis of outcome measures derived from subsets of study patients: a children and b hypotensive patients. The dotted line represents the theoretical plot of a test with no discrimination

positive findings (positive LR 17·35 (95 per cent c.i. 8·97–33·53)), but appeared to be even worse with regard to the exclusion of organ lacerations (negative LR 0·32 (95 per cent c.i. 0·22–0·45)).

Evaluation of three trials containing 155 patients allowed some inference on the value of ultrasonography in situations of haemodynamic instability[44,50,56]. The pooled ROC curve extends to a robust Q* value of 0·89 (95 per cent c.i. 0·13–1·64) (*Fig. 4b*). For a prevalence of 30 per cent among all three investigations, NPVs ranged from 0·93 to 0·98. The corresponding positive and negative LRs were calculated as 11·60 (95 per cent c.i. 5·48–24·56) and 0·14 (95 per cent c.i. 0·07–0·31). Outcome measures were distributed homogeneously, and fixed effects modelling remained appropriate. Follow-up examinations were carried out only in selected cases, with too few data available for adequate subset analysis.

Finally, the diagnostic power of ultrasonography with different reference standards was compared. No subset analysis could be performed on clinical observation only. SROC curves are presented in *Fig. 5*. Higher Q* values were computed comparing ultrasonography with diagnostic peritoneal lavage than with CT (0·93 (95 per cent c.i. 0·80–1·05) *versus* 0·88 (95 per cent c.i. 0·76–1·00)). NPVs ranged from 0·78 to 0·97 (prevalence 0·25–0·65), and from 0·84 to 0·98 (prevalence 0·10–0·65) respectively. When peritoneal lavage was used as the diagnostic gold standard,

Table 3 Results of included studies investigating the diagnostic value of emergency ultrasonography for the detection of organ injury

Reference	Year	NPV	Sensitivity	Specificity	AUROC	Accuracy	LR +	LR –
Akgür *et al.*[2]	1997	0·95 (0·92–0·98)	0·84 (0·79–0·89)	0·99 (0·98–1·00)	0·92 (0·86–0·98)	0·96 (0·93–0·98)	88·33 (17·88–436·42)	0·17 (0·09–0·31)
Froelich *et al.*[77]	1992	0·81 (0·66–0·96)	0·87 (0·74–1·00)	0·91 (0·80–1·02)	0·89 (0·75–1·00)	0·88 (0·76–1·01)	6·75 (1·49–30·61)	0·18 (0·06–0·57)
Förster *et al.*[33]	1992	0·99 (0·97–1·01)	0·97 (0·94–1·00)	0·96 (0·93–0·99)	0·96 (0·92–1·00)	0·96 (0·93–1·00)	23·64 (9·53–58·68)	0·05 (0·01–0·25)
Goletti *et al.*[34]	1994	0·90 (0·84–0·97)	0·87 (0·79–0·94)	0·98 (0·94–1·01)	0·92 (0·84–1·00)	0·93 (0·87–0·99)	25·08 (5·17–121·68)	0·15 (0·06–0·35)
Healey *et al.*[64]	1996	0·99 (0·98–1·00)	0·88 (0·86–0·90)	0·98 (0·97–0·99)	0·93 (0·88–0·98)	0·97 (0·96–0·98)	37·30 (23·21–59·93)	0·13 (0·06–0·26)
Katz *et al.*[55]	1996	0·98 (0·96–1·01)	0·91 (0·86–0·96)	0·84 (0·77–0·90)	0·87 (0·77–0·98)	0·84 (0·78–0·91)	5·25 (3·29–8·38)	0·15 (0·03–0·67)
Krupnick *et al.*[41]	1997	0·72 (0·61–0·83)	0·62 (0·50–0·74)	0·98 (0·96–1·01)	0·80 (0·68–0·91)	0·80 (0·71–0·90)	41·00 (2·59–650·16)	0·38 (0·25–0·60)
McGahan *et al.*[35]	1997	0·85 (0·78–0·91)	0·63 (0·55–0·72)	0·95 (0·91–0·99)	0·79 (0·69–0·89)	0·85 (0·79–0·91)	11·73 (4·62–29·74)	0·39 (0·26–0·59)
McKenney *et al.*[76]	1998	0·98 (0·97–0·99)	0·86 (0·84–0·89)	0·99 (0·99–1·00)	0·93 (0·89–0·97)	0·98 (0·97–0·99)	102·58 (47·53–221·38)	0·14 (0·09–0·22)
Röthlin *et al.*[36]	1993	0·89 (0·86–0·93)	0·44 (0·38–0·49)	1·00 (0·99–1·00)	0·72 (0·63–0·81)	0·90 (0·86–0·93)	75·54 (73·92–382·90)	0·57 (0·45–0·71)
Singh *et al.*[52]	1997	0·78 (0·68–0·87)	0·74 (0·64–0·84)	0·87 (0·79–0·95)	0·81 (0·70–0·91)	0·81 (0·72–0·90)	5·22 (2·35–11·60)	0·31 (0·18–0·54)

Values in parentheses are 95 per cent confidence intervals. NPV, negative predictive value; AUROC, area under the receiver operating characteristic curve; LR +, likelihood ratio for positive findings; LR –, likelihood ratio for negative findings

Table 4 Results of included studies investigating the diagnostic value of emergency ultrasonography for the detection of free fluid

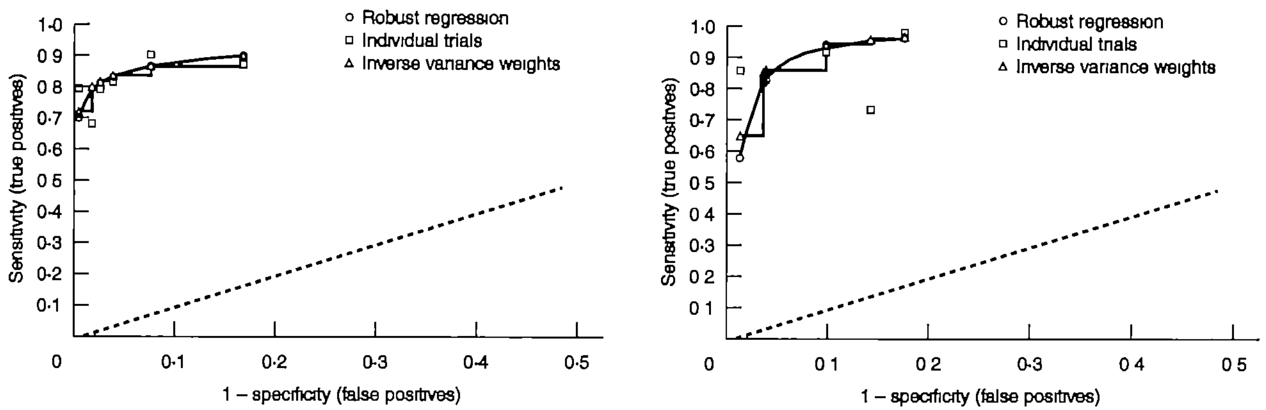
Reference	Year	NPV	Sensitivity	Specificity	AUROC	Accuracy	LR +	LR –
Ballard *et al.*[37]	1999	0·85 (0·78–0·92)	0·28 (0·19–0·36)	0·99 (0·98–1·01)	0·63 (0·47–0·78)	0·86 (0·79–0·92)	46·20 (2·66–801·69)	0·73 (0·56–0·96)
Boulanger *et al.*[42]	1996	0·96 (0·94–0·98)	0·81 (0·77–0·85)	0·97 (0·95–0·98)	0·89 (0·83–0·95)	0·94 (0·92–0·97)	23·65 (13·23–42·27)	0·20 (0·12–0·33)
Chiu *et al.*[7]	1997	0·98 (0·97–0·99)	0·71 (0·68–0·74)	1·00 (1·00–1·00)	0·86 (0·78–0·93)	0·98 (0·97–0·99)	1020·28 (63·53–16 385·19)	0·29 (0·19–0·44)
Coley *et al.*[54]	2000	0·78 (0·70–0·86)	0·38 (0·28–0·47)	0·97 (0·94–1·00)	0·67 (0·55–0·80)	0·79 (0·72–0·87)	11·52 (3·15–42·04)	0·64 (0·49–0·84)
Hoffmann *et al.*[47]	1992	0·93 (0·90–0·96)	0·89 (0·86–0·93)	0·97 (0·95–0·99)	0·93 (0·89–0·97)	0·94 (0·91–0·97)	24·74 (11·60–52·78)	0·12 (0·07–0·20)
Ingeman *et al.*[43]	1996	0·92 (0·86–0·97)	0·75 (0·66–0·84)	0·96 (0·92–1·00)	0·85 (0·75–0·96)	0·91 (0·85–0·96)	15·65 (5·48–44·65)	0·27 (0·14–0·53)
Kern *et al.*[63]	1997	0·98 (0·97–0·99)	0·73 (0·70–0·77)	0·98 (0·96–0·99)	0·85 (0·76–0·95)	0·96 (0·94–0·98)	28·39 (15·76–51·14)	0·28 (0·16–0·50)
Liu *et al.*[53]	1993	0·84 (0·74–0·94)	0·92 (0·84–0·99)	0·95 (0·89–1·01)	0·93 (0·85–1·00)	0·93 (0·86–1·00)	12·07 (2·58–56·46)	0·10 (0·04–0·28)
McElveen *et al.*[38]	1997	0·96 (0·92–1·00)	0·88 (0·80–0·95)	0·98 (0·96–1·01)	0·93 (0·83–1·00)	0·96 (0·92–1·00)	38·10 (7·73–187·68)	0·15 (0·05–0·47)
McKenney *et al.*[46]	1994	0·96 (0·94–0·99)	0·83 (0·78–0·88)	0·99 (0·98–1·00)	0·91 (0·84–0·99)	0·97 (0·94–0·99)	90·69 (18·30–449·37)	0·18 (0·09–0·37)
McKenney *et al.*[39]	1996	0·98 (0·97–0·99)	0·88 (0·86–0·90)	0·99 (0·98–1·00)	0·94 (0·90–0·97)	0·97 (0·96–0·98)	87·44 (44·67–171·14)	0·12 (0·08–0·19)
Rozycki *et al.*[79]	1993	0·95 (0·93–0·97)	0·79 (0·75–0·83)	0·96 (0·94–0·97)	0·87 (0·82–0·92)	0·92 (0·90–0·95)	17·38 (10·86–27·81)	0·22 (0·15–0·33)
Rozycki *et al.*[54]	1995	0·98 (0·96–0·99)	0·90 (0·87–0·93)	1·00 (0·99–1·00)	0·95 (0·90–0·99)	0·98 (0·97–0·99)	182·40 (36·89–902·87)	0·11 (0·05–0·22)
Rozycki *et al.*[66]	1998	0·99 (0·98–0·99)	0·78 (0·76–0·81)	1·00 (1·00–1·00)	0·89 (0·83–0·95)	0·99 (0·98–0·99)	360·05 (103·77–1249·20)	0·22 (0·14–0·34)
Shackford *et al.*[65]	1999	0·92 (0·88–0·95)	0·69 (0·63–0·75)	0·98 (0·97–1·00)	0·83 (0·76–0·91)	0·92 (0·88–0·95)	35·89 (12·51–102·98)	0·32 (0·22–0·48)
Thomas *et al.*[80]	1997	0·98 (0·97–1·00)	0·81 (0·77–0·85)	0·99 (0·98–1·00)	0·90 (0·80–1·00)	0·98 (0·96–1·00)	89·09 (25·47–311·62)	0·21 (0·09–0·47)
Tso *et al.*[45]	1992	0·96 (0·94–0·99)	0·69 (0·62–0·76)	0·99 (0·98–1·01)	0·84 (0·70–0·98)	0·96 (0·93–0·99)	66·75 (13·13–339·23)	0·33 (0·16–0·65)
Wherrett *et al.*[44]	1996	0·93 (0·87–0·99)	0·85 (0·77–0·93)	0·90 (0·83–0·97)	0·87 (0·77–0·98)	0·88 (0·81–0·96)	7·58 (3·37–17·05)	0·19 (0·07–0·49)
Yeo *et al.*[40]	1999	0·93 (0·84–1·01)	0·67 (0·52–0·82)	0·97 (0·91–1·02)	0·82 (0·58–1·00)	0·92 (0·84–1·01)	14·14 (2·69–74·25)	0·37 (0·14–1·01)

Values in parentheses are 95 per cent confidence intervals. NPV, negative predictive value; AUROC, area under the receiver operating characteristic curve; LR +, likelihood ratio for positive findings; LR –, likelihood ratio for negative findings

Table 5 Subset analysis of data gained from Röthlin *et al.*[36]

	Prevalence	NPV	Sensitivity	Specificity	Accuracy	LR +	LR –
Injured organ							
Spleen	0·07	0·95 (0·93–0·98)	0·37 (0·32–0·42)	0·99 (0·99–1·00)	0·95 (0·92–0·97)	71·94 (13·37–387·21)	0·63 (0·46–0·87)
Liver	0·03	0·97 (0·95–0·99)	0·15 (0·11–0·19)	1·00 (0·99–1·00)	0·97 (0·95–0·99)	30·50 (3·47–268·14)	0·85 (0·66–1·11)
Kidney	0·03	0·97 (0·95–0·99)	0·23 (0·18–0·27)	1·00 (0·99–1·00)	0·97 (0·95–0·99)	46·06 (6·67–318·23)	0·78 (0·56–1·07)
Small bowel	0·01	0·99 (0·98–1·00)	0·38 (0·32–0·43)	1·00 (0·99–1·00)	0·99 (0·97–1·00)	77·75 (10·14–596·16)	0·63 (0·29–1·34)
Free fluid							
Beginners	0·16	0·99 (0·97–1·01)	0·93 (0·89–0·97)	1·00 (0·99–1·01)	0·99 (0·97–1·01)	228·09 (14·32–3633·69)	0·07 (0·01–0·31)
Experts	0·19	1·00 (0·99–1·01)	0·98 (0·97–1·00)	1·00 (0·99–1·01)	0·99 (0·98–1·01)	271·69 (17·07–4323·54)	0·02 (0·00–0·25)
Organ lacerations							
Beginners	0·18	0·88 (0·83–0·93)	0·37 (0·29–0·44)	1·00 (0·99–1·01)	0·88 (0·83–0·94)	87·69 (5·27–1459·60)	0·64 (0·48–0·85)
Experts	0·19	0·88 (0·83–0·93)	0·45 (0·38– 0·53)	0·99 (0·98–1·01)	0·89 (0·84–0·94)	62·27 (8·53–454·77)	0·55 (0·40–0·75)

Values in parentheses are 95 per cent confidence intervals. NPV, negative predictive value; LR +, likelihood ratio for positive findings; LR –, likelihood ratio for negative findings



a Reference standard: computed tomography

b Reference standard: peritoneal lavage

Fig. 5 Summary receiver operating characteristic curves obtained from robust and weighted regression analysis of outcome measures comparing different reference standards: **a** computed tomography and **b** peritoneal lavage. The dotted line represents the theoretical plot of a test with no discrimination

ultrasonography had a substantial impact on pretest probabilities, with a positive LR of 10·83 (95 per cent c.i. 6·45–18·17) and a negative LR of 0·11 (95 per cent c.i. 0·06–0·21). This advantage diminished when ultrasonography was compared with CT. While positive LRs still indicated a relevant increase in diagnostic certainty in confirming the presence of abdominal injuries (positive LR 11·42 (95 per cent c.i. 8·01–16·29)), the ability of ultrasonography to exclude lacerations remained below clinically acceptable threshold levels (negative LR 0·21 (95 per cent c.i. 0·16–0·29)).

Assessment of suspected stage migration

Linear regression analysis, adjusted for publication year, sample size, prevalence, NPV, areas under the ROC curve and LRs, failed to demonstrate any statistically significant change in diagnostic accuracy of emergency ultrasonography during the past 20 years. This was true both for the detection of free fluid (R^2 = 0·158, P = 0·092) and for the recognition of organ injuries (R^2 = 0·021, P = 0·668).

Discussion

The true frequency of blunt abdominal trauma is unknown. According to the National Center for Health Statistics, over 20 000 patients were discharged in 1997 from short hospital stay in the USA because of blunt injuries of the liver and spleen[57]. Correct assessment of the injury pattern caused by blunt forces remains one of the challenges of trauma care. Patients without suspicious clinical findings might have sustained haematomas of solid viscera, mesenteric tears or hollow organ lacerations that carry a risk of detrimental complication if missed initially[58–62]. Missed hepatic and splenic ruptures accounted for the majority of emergency department deaths (37 per cent) in an autopsy study conducted by Hodgson *et al.*[4]. Emergency ultrasonography was regarded as a promising new approach to tackling these issues and has gained increasing acceptance since its introduction in the late 1980s. Of all the clinically utilized imaging modalities, it has several unique features. Its potential advantages (availability, easy and quick handling, repeatability and cost effectiveness) depend strongly on technical standards, patient-related variables (e.g. abdominal wall thickness), examination conditions and expertise.

While all but one of the studies presently included in the final model were described as prospective trials, the true prospective nature of inclusion criteria (e.g. only inpatients with a minimum of 23 h of observation[51,56]), the frequency of reference standard application to prove the ultrasonographic findings[36,63], and reasons for the exclusion of certain patients seemed questionable in some instances[45,64]. Other concerns arise from occasional discrepancies between data presented in the abstract and those of the body of the article[35]. Study quality is always a major issue in meta-analysis; while it was not the aim of this investigation unreasonably to criticize methodological weaknesses (but rather to gain insight on the clinically important findings within the pooled data) the results suggest a significant bias inherent in the majority of studies. Such bias might lead to an overestimation of the diagnostic power of emergency ultrasonography.

The learning curve of the FAST protocol is expected to be steeper for the detection of free fluid than for the detection of visceral lesions. Shackford and colleagues[65] observed a significant decrease in failure rates in screening for haemoperitoneum after only ten examinations performed by trauma surgeons. However, diagnostic precision did not differ remarkably with respect to both SROC curves and probability nomograms. Perhaps surprisingly, results were not influenced by the steady improvement of sonographic resolution properties over the past 20 years in the linear regression model. To be blunt, ultrasonography itself, as well as the amount of useful experience gained by routine application of the technique, has already reached its limits in the emergency setting.

A high degree of sensitivity is not useful to rule *in* a diagnosis, but rather to rule *out* a particular condition. Similarly, high levels of specificity indicate that positive findings will detect the presence of a disorder. The sensitivity of ultrasonography for either endpoint ranged from 28 to 97 per cent, while the specificity was calculated as close to 100 per cent within individual trials. While these data look impressive at a first glance, the need for caution is clear when the detail is examined. The true clinical problem associated with torso trauma is not to determine the presence of an organ lesion, but precisely to exclude intra-abdominal injuries. Definitive abdominal evaluation is most difficult in unconscious subjects[60]. The results of the present meta-analysis have revealed remarkable weaknesses in emergency ultrasonography with respect to these issues.

A summary measure of 0·90 was calculated for the sensitivity–specificity pair closest to the desirable upper left corner of the ROC curve. This means that every tenth abdominal organ injury will be missed by initial ultrasonographic diagnostics. There are other convenient measures of test efficacy outlining the precariousness that arises from an innocuous primary sonogram: the NPV, and the post-test probability calculated as a function of the negative LR. The NPV indicates the percentage of correct diagnoses among all negative findings. Obviously, the NPV decreases linearly with increasing prevalence, with a steeper negative slope of the fitted regression line for the exclusion of organ lesions than for free fluid. This might not be of relevance for the general surgeon who treats a victim of blunt abdominal trauma once a month, but it could strongly influence the diagnostic decision tree of a busy emergency department. For a prevalence of 30 per cent (which is relevant to urban areas), the NPV of ultrasonography falls rapidly below 90 per cent. It must be emphasized that the term prevalence does not only describe the frequency of a particular disorder but also reflects the chance of an individual subject being diseased or injured (pretest probability). If the pretest probability for the presence of a visceral laceration gained from clinical judgement alone is 50 per cent (e.g. in an unconscious car accident victim presenting with abdominal belt marks), a probability of nearly 25 per cent will remain despite negative ultrasonographic findings. With regard to common LRs above 0·2 for both pathologies (i.e. free fluid and organ lesions), a negative sonogram is of only minor value in achieving certainty about the consequences of blunt abdominal trauma[66,67].

Relatively low sensitivity and NPVs, as well as negative LRs and associated post-test probabilities out of the clinically acceptable range, prevent belief in negative sonographic findings, whereas high specificity and positive LRs above 10 mean that positive results prove the presence of intra-abdominal injury. Whether the initial sonogram is positive or negative for free fluid or organ lesions, clinically suspected blunt abdominal trauma requires further diagnostic evaluation. Positive ultrasonographic results might allow a patient to be scheduled for emergency surgery in situations of haemodynamic instability that is refractory to any resuscitation effort[68–70]. On the other hand, standardized protocols can decrease the examination time of helical CT to minutes, thereby enabling a definite and simultaneous assessment of parenchymal viscera, large vessels, lumbar spine and hollow organs[21,71,72].

The authors conclude that trauma algorithms need to be revisited for the sense and non-sense of the use of ultrasonography in the trauma setting, and for the need of another diagnostic reference standard. Evidence-based trauma management must consider local realities and expertise[58,73,74]. While an initial CT scan should be recommended as the diagnostic modality of choice in level I trauma centres[75,76], the present meta-analysis provides a rationale for surgeons to advocate at least clinical observation regardless of sonographic results in patients with suspected blunt abdominal injuries.

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Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery

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Background: Low molecular weight heparins (LMWHs) have become routine thromboprophylaxis in general surgery. However, their actual clinical effect, its magnitude relative to that of unfractionated heparin (UFH), and the optimal dose are still debated.
Methods: A meta-analysis was performed of all available randomized trials in general surgery comparing LMWH with placebo or no treatment, or with UFH.
Results: Comparison *versus* placebo or no treatment confirmed that the significant reduction in asymptomatic deep vein thrombosis (DVT) obtained with LMWH ($n = 513$; relative risk (RR) 0·28 (95 per cent confidence interval 0·14–0·54)) was associated with a significant reduction in clinical pulmonary embolism ($n = 5456$; RR 0·25 (0·08–0·79)) and clinical venous thromboembolism (VTE) ($n = 4890$; RR 0·29 (0·11–0·73)), and a trend towards a reduction in overall mortality rate. Comparison *versus* UFH showed a trend in favour of LMWH, with a significant reduction in clinical VTE ($P = 0·049$), a trend also found for cancer surgery. LMWH at doses below 3400 anti-Xa units seemed to be as effective as, and safer than, UFH, while higher doses yielded slightly superior efficacy but increased haemorrhagic risk, including that of major haemorrhage.
Conclusion: Asymptomatic DVT may be regarded as a reliable surrogate endpoint for clinical outcome in studies investigating thromboprophylaxis in general surgery. LMWH seems to be as effective and safe as UFH. Determination of the optimal dose regimen of LMWH for this indication requires further investigation.

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Introduction

Low molecular weight heparins (LMWHs) have become the reference treatment for venous thromboembolism (VTE) prophylaxis in patients undergoing general surgery, mainly on the basis of their ability to reduce the incidence of deep vein thrombosis (DVT) detected systematically using an objective test at the end of the treatment period[1,2]. However, the clinical relevance of a reduction in asymptomatic DVT has been questioned, as it has never been demonstrated in a single clinical study that this is associated with a reduction in the incidence of clinically important VTE[3]. If it is assumed that the reason for this is a lack of statistical power owing to inadequate sample size, meta-analysis may be an appropriate tool to recognize the clinical efficacy of LMWHs in general surgery, as well as their effects on other clinical endpoints such as major haemorrhage or overall mortality rate. Only two rather dated meta-analyses of LMWH *versus* placebo or no treatment have addressed this issue. They showed that a reduction in the risk of asymptomatic DVT was associated with a reduction in the risk of pulmonary embolism (PE) or death[4,5]; this has also been found for other prophylactic indications for both LMWH and unfractionated heparin (UFH)[4–8]. It is now worthwhile to update these two meta-analyses with more recent studies.

The effect of LMWH relative to that of UFH varies between the available meta-analyses, which included different numbers of studies[4,5,9–12]. This may be explained by the different criteria used to select studies, and different exhaustivity in terms of the number of studies included compared with the total number potentially eligible at the time the meta-analysis was performed. Exhaustivity has been postulated to be a critical factor for the validity and interpretation of meta-analyses[13]. Furthermore, the number of published studies conducted in patients undergoing surgery for cancer should now allow the evaluation of LMWH in this subgroup of patients who are considered to be at high risk of both VTE and haemorrhage[1,2]. The optimal dose of LMWH to be used for thromboprophylaxis in general surgery remains controversial; both low and high doses have been proposed by various manufacturers. According to some authors, a daily subcutaneous dose of more than 3400 anti-Xa units yields no additional benefit in terms of efficacy while leading to an increased haemorrhagic risk[1,10,11].

In the light of the above, a meta-analysis was carried out with three specific objectives in mind. (1) To verify the clinical effect of LMWH from data obtained from all available randomized clinical trials comparing a LMWH with placebo or no treatment, or with UFH, in patients undergoing general surgery. (2) To evaluate this effect in patients undergoing surgery for cancer. (3) To assess the efficacy and safety of low and high prophylactic doses of LMWH in this setting.

Methods

Literature search

An exhaustive literature search, both manual and computer assisted (Medline® and Current Contents®) was performed, encompassing randomized studies comparing a prophylactic regimen of LMWH with any other prophylactic treatment in patients undergoing general surgery, defined as abdominothoracic (excluding vascular), urological and gynaecological surgery, as well as surgery for malignant disease. There was no restriction on the language of the article. The following keywords were used: general surgery, abdominal surgery, cancer surgery, heparin, low molecular weight heparin, postoperative complications, prophylaxis, controlled trial, randomized trial, venous thromboembolism, deep vein thrombosis, pulmonary embolism and mortality. Abstracts of meetings were searched and reference lists in reviews, studies and previous meta-analyses were checked. Particular attention was paid to duplicate reports; when studies were published as an abstract and an original article, only the latter was considered. When more than one article was available from a single study, an attempt was made to extract the information required from all relevant publications. All citations have been included in the list of references.

Study selection

From these articles, open-label, single- or double-blind randomized studies evaluating a LMWH were selected. Only studies with a control group, either untreated or treated with a placebo, or with low-dose UFH, were considered. Studies that included dihydroergotamine or elastic stockings were eligible. Included studies were required to evaluate the efficacy and/or safety of a LMWH using at least one of the following criteria: DVT detected by a systematic objective test, PE, major haemorrhage or death.

Studies were excluded if they were not randomized or clearly stated as such, conducted according to a 'play-the-winner design', or conducted in patients undergoing orthopaedic surgery, non-cancer thoracic surgery, extracorporeal circulation surgery or non-cancer laparoscopic surgery. Dose-ranging studies without a control group given placebo or no treatment, or UFH, for comparison were excluded, as were studies involving heparinoids.

Collection of data

Predefined data from individual trials were initially extracted independently by three of the authors (P.M., S.L., J.-Y.D.). A concordance meeting was organized and, in cases of discrepancy regarding either study selection or data extraction, agreement was reached. The following study characteristics were recorded: name of the first author or study acronym, year(s) of publication, number of patients randomized, indication for surgery (general, abdominal, gynaecological or cancer surgery), percentage of patients undergoing surgery for cancer and, if there was a stratification of patients with cancer, the type, duration and dose regimens of treatments, and whether they were administered before or after operation, in an open-label, single- or double-blind fashion, the type of anaesthesia (general or regional), the method used to detect DVT and at which time point, and the duration of follow-up.

Endpoints

The primary endpoint was the incidence of DVT detected systematically by ultrasonography, fibrinogen uptake test, impedance plethysmography, thermography or venography at the end of the treatment period or earlier in cases of clinical suspicion. Positive results of impedance plethysmography or thermography had to be confirmed by venography.

Secondary endpoints were the incidence of symptomatic PE (both non-fatal and fatal), symptomatic VTE (DVT and/or PE), death, major haemorrhage, wound haematoma and other haemorrhage (excluding haematoma at the injection site) and the percentage of patients requiring postoperative transfusion (if available, otherwise the percentage of patients requiring transfusion irrespective of time it was used). The definitions of major haemorrhage used in the original articles were heterogeneous. Whenever available, the author's definition was used. Otherwise, haemorrhage leading to death, blood transfusion, reoperation or permanent discontinuation of the treatment under assessment was considered as a major haemorrhage. The incidences of symptomatic VTE and death were derived from the complete period of follow-up, not just that of thromboprophylaxis or hospital stay. Haemorrhagic endpoints were recorded at the end of the treatment period.

Statistical analysis

The results from each trial were summarized on an intention-to-treat basis in two-by-two tables for each endpoint. The denominator used for estimating the incidence of DVT was the number of patients who had undergone a systematic detection test at the end of the treatment period (available patients). For all other endpoints, the denominator was the number of randomized patients in each treatment group.

Two meta-analyses were performed, the first using data from trials comparing LMWH with no treatment or placebo, and the second using data from trials comparing LMWH with UFH. The meta-analyses were performed using a variety of methods: logarithm of the relative risk (RR), logarithm of the odds ratio, Mantel Haenszel, Cochran and Peto[13]. Since the results obtained were similar, only those from the logarithm of the RR method are presented. A RR of 1 indicates no difference between the treatments, less than 1 that LMWH is better, and more than 1 that the control treatment (either no treatment or placebo, or UFH) is better. Association and heterogeneity tests were performed for each meta-analysis. $P \leqslant 0{\cdot}05$ from an association test and a $P \leqslant 0{\cdot}10$ from a heterogeneity test were considered as statistically significant. In the absence of a clear explanation for heterogeneity, a random-effect model for the RR was planned. Meta-analyses were performed using the software EasyMA® (University Claude Bernaud, Lyon, France)[14,15]. Results from these meta-analyses are presented graphically including RRs with 95 per cent confidence intervals (c.i.).

Two sensitivity analyses were performed, the first dealing with studies in which LMWH was given in combination with dihydroergotamine and the second according to the UFH dose regimen (5000 units twice daily *versus* 5000 units three times daily). Subgroup analyses were performed for studies that were well identified double-blind trials, for cancer surgery (studies with over 90 per cent of patients undergoing cancer surgery or data from studies with a cancer surgery stratum), for non-cancer surgery, and for LMWH dose regimens of 3400 anti-Xa units or less and more than 3400 anti-Xa units.

Results

A total of 82 studies, from 1984 to 1999, evaluating the thromboprophylactic effect of LMWH in general surgery was identified. Of these, 21 were excluded for the following reasons: absence or uncertainty of randomization in six studies[16–21], play-the-winner design in two studies[22,23], comparison of LMWHs in seven studies[24–30], use of a heparinoid in two studies[31,32], and incomplete[33,34] or unpublished results (Samama 1990 and Koppenhagen 1990) in four studies. Fifty-nine studies were therefore selected, eight comparing a LMWH with placebo or no treatment[35–43] and 51 comparing a LMWH with UFH[44–103].

Low molecular weight heparin *versus* placebo or no treatment

Description of studies

The eight studies contained 5520 patients; six were double blind[35–40,42] and two were open[41,43] (*Table 1*). The LMWHs used were nadroparin (three studies, 4751 patients), enoxaparin (two studies, 392 patients), dalteparin (one study, 197 patients), parnaparin (one study, 100 patients) and tinzaparin (one study, 80 patients). Two studies, both open, were conducted in cancer surgery[41,43]. DVT was detected systematically at the end of the treatment period in five studies (513 patients); clinical efficacy and safety endpoints were available for 4890–5456 patients (*Table 2*).

Results

In the placebo or no treatment group, the adjusted incidences of events(S.D.) were 14·5(2·2) per cent for systematically detected DVT, 0·5(0·1) per cent for clinical PE, 0·9(0·2) per cent for clinical VTE and 0·9(0·2) per cent for death. A statistically significant 72 per cent reduction in the risk of DVT was observed in the LMWH group (RR 0·28 (95 per cent c.i. 0·14–0·54); $P < 0{\cdot}001$). This reduction was associated with similar significant reductions in the risk of clinical endpoints, 75 per cent for clinical PE (RR 0·25 (0·08–0·79); $P = 0{\cdot}018$) and 71 per cent for clinical VTE (RR 0·29 (0·11–0·73); $P = 0{\cdot}009$), and with a non-significant 46 per cent reduction in overall mortality rate (RR 0·54 (0·27–1·10); $P = 0{\cdot}09$) (*Fig. 1*).

Haemorrhage was more frequent in LMWH-treated than in placebo-treated patients, with an increase of 103 per cent for major haemorrhage, 106 per cent for total haemorrhage, 88 per cent for wound haematoma and 53

Table 1 Low molecular weight heparin *versus* placebo or no treatment: description of studies

Reference	Year	Type of surgery	Cancer surgery (%)	LMWH and dose (anti-Xa units)	Control group	Study design	Time of first administration	Type of anaesthesia	Treatment duration (days)	Diagnosis of DVT*	Follow-up duration	Patients randomized
Le Gagneux *et al.*[35]	1987	Prostatectomy	n.a.	Enoxaparin 6000	Placebo	Blind	Preop. 12 h	n.a.	n.a.	FUT + veno.	n.a.	89
Valle *et al.*[36]	1988	Abdominal and breast	n.a.	Parnaparin 3200	Placebo	Blind	Preop. 2 h	General	7	US + veno.	n.a.	100
Ockelford *et al.*[37]	1989	Abdominal	43	Dalteparin 2500	Placebo	Blind	Preop. 1–2 h	General	5–9	FUT	6 weeks	197
Pezzuoli *et al.*[38,39] (STEP)	1989–1990	General	33	Nadroparin 2850	Placebo	Blind	Preop. 2 h	n.a.	> 7	Not evaluated	3 weeks	4498
Balas *et al.*[40]	1992	General	n.a.	Nadroparin 2850	Placebo	Blind	Preop. 12 h	General	5–8	Veno. but n.a.	n.a.	189†
Marassi *et al.*[41]	1993	Abdominal	100	Nadroparin 2850	No treatment	Open	Preop. 2 h	n.a.	7	FUT + veno.	7 days	64
Bergqvist *et al.*[42]	1996	Abdominal	n.a.	Tinzaparin 3500	Placebo	Blind	Postop.	n.a.	> 5	FUT + veno.	1 month	80
Ho *et al.*[43]	1999	Colorectal	94	Enoxaparin 4000	No treatment	Open	Preop. 12 h	n.a.	> 4	Not evaluated	9 months	303†

*At end of the treatment. †No. of patients for whom the group distribution was available. LMWH, low molecular weight heparin; DVT, deep vein thrombosis; n.a., data not available; preop., before operation; postop., after operation; FUT, fibrinogen uptake test; veno, DVT confirmed by venography; US, ultrasonography; STEP, studio embolia polmonare

Table 2 Low molecular weight heparin *versus* placebo or no treatment: incidence of all evaluation criteria in each treatment group

		Patients randomized		Asymptomatic DVT*		Clinical PE		Clinical thrombo-embolism		Death		Major haemorrhage		Total haemorrhage		Wound haematoma		Transfusion	
Reference	Year	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C	LMWH	C
Le Gagneux *et al.*[35]	1987	44	45	0/44	0/45	0	0	0	0	n.a.	n.a.	0	0	n.a.	n.a.	n.a.	n.a.	8	6
Valle *et al.*[36]	1988	50	50	0/50	3/50	0	0	n.a.	n.a.	n.a.	n.a.	0	0	0	1	0	1	5	5
Ockelford *et al.*[37]	1989	102	95	4/95	14/88	0	2	n.a.	n.a.	0	2	4	4	10	4	2	0	n.a.	n.a.
Pezzuoli *et al.*[38,39] (STEP)	1989–1990	2247	2251	n.a.	n.a.	(2)	(8)	5	17	8	18	67	30	439	210	265	141	221	134
Balas *et al.*[40]	1992	94	95	n.a.	n.a.	0	1	n.a.	n.a.	n.a.	n.a.	0	2	4	7	n.a.	n.a.	n.a.	n.a.
Marassi *et al.*[41]	1993	31	33	2/30	11/31	n.a.	n.a.	n.a.	n.a.		0	n.a.	n.a.	0	1	0	1	14	13
Bergqvist *et al.*[42]	1996	39	41	3/39	9/41	0	1	n.a.	n.a.	0	2	1	0	2	0	0	0	n.a.	n.a.
Ho *et al.*[43]	1999	134	169	n.a.	n.a.	0	3	0	5	3	2	3	1	9	3	2	0	25	22
Total no. of studies†		8		5		7		3		5		7		7		6		5	
Total no. of patients†		5520		513		5456		4890		5142		5456		5431		5242		5054	

Values in parentheses are cases of fatal pulmonary embolism (PE). *Denominator is number of patients who had a systematic detection test for asymptomatic deep vein thrombosis (DVT) at the end of the treatment period. †Combined total numbers for low molecular weight heparin (LMWH) and control (C; placebo or no treatment) groups. n.a., Data not available; STEP, studio embolia polmonare

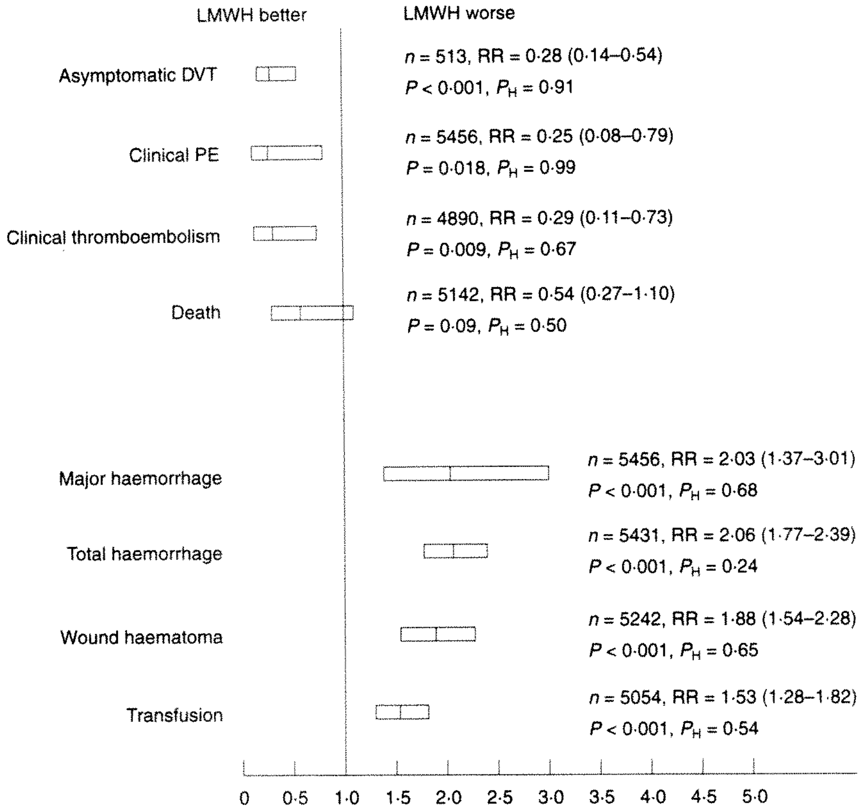

Fig. 1 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with placebo or no treatment. The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than placebo or no treatment. If the value of 1 is included in the box, the result is not significant ($P > 0.05$). P_H indicates the result of the heterogeneity test. DVT, deep vein thrombosis; PE, pulmonary embolism

per cent for the number of patients requiring postoperative transfusion ($P < 0.001$ for all criteria) (*Fig. 1*). For instance, the incidence of major haemorrhage was 2·8(0·3) per cent and that of wound haematoma 10·3(0·6) per cent in the LMWH group. Owing to the small number of studies, subgroup analyses were not performed.

Low molecular weight heparin *versus* unfractionated heparin

Description of studies

The 51 studies involved contained 48 624 patients (*Table 3*). The principal LMWHs were certoparin (15 studies, 27 707 patients, including one study with 23 078 patients), dalteparin (13 studies, 6803 patients), enoxaparin (eight studies, 6017 patients), nadroparin (five studies, 3220 patients), and parnaparin (four studies, 492 patients). Only one study each was identified for other LMWHs. LMWH was administered before operation in 50 of the 51 studies. UFH was given at the dose of 5000 units three times daily in 20 studies, 5000 units twice daily in 30 studies and 2500 units twice daily in one study. Eight studies, including the cancer stratum of the European Fraxiparin Study, involved the treatment of cancer[48,53–55,73,91,100–102]. Thirty-three studies were double blind. DVT was detected systematically at the end of the treatment period in 41 studies (17 995 patients), and the clinical efficacy and safety endpoints were available for 13 776 to 46 646 patients (*Table 4*).

Results

In the UFH group the adjusted incidences of events were 5·0(0·2) per cent for systematically detected DVT, 0·4(0·0) per cent for clinical PE, 1·3(0·1) per cent for clinical VTE and 1·7(0·1) per cent for death. A non-significant 10 per cent reduction in the risk of DVT was observed in the LMWH group (RR 0·90 (0·79–1·02); $P = 0.10$) as well as a non-significant 12 per cent reduction in the risk of clinical PE

Table 3 Low molecular weight heparin *versus* unfractionated heparin: description of studies

Reference	Year	Type of surgery	Cancer surgery (%)	LMWH and dose (anti-Xa units)	UFH (units)	Study design	Time of first administration	Type of anaesthesia	Treatment duration (days)	Diagnosis of DVT*	Follow-up duration	Patients randomized
Schmitz-Huebner *et al.*[44]	1984	Abdominal	n.a.	Certoparin (dose 1 and dose 2) b.i.d.	10 000	Blind	Preop. 2 h	General	7	FUT	1 month	126
Törngren *et al.*[45]	1984	General	n.a.	SSHA 50 mg and 37·5 mg	10 000	Blind	Preop. 2 h	General	7	FUT	Discharge	471
Kakkar and Murray[46]	1985	General	31	Nadroparin 2850	10 000	Blind	Preop. 2 h	n.a.	7	FUT	10 days	400
Bergqvist *et al.*[47]	1986	Abdominal	45	Dalteparin 5000	10 000	Blind	Preop. 2 h	General or regional	5–7	FUT	1 month	432†
Onarheim *et al.*[48]	1986	Abdominal	100	Dalteparin 5000	10 000	Blind	Preop. 2 h	General	6	FUT + veno.	1 month	52
Sasahara *et al.*[49]	1986	Abdominal	n.a.	Certoparin 3000 + DHE	10 000 + DHE	Blind	Preop. 2 h	n.a.	7	FUT + veno.	7 days	269
Voigt *et al.*[50]	1986	Abdominal	41	Certoparin 3000 + DHE	10 000 + DHE	Blind	Preop. 2 h	General	> 7	Not evaluated	10 days	200†
Koller *et al.*[51,52]	1986	Abdominal	n.a.	Dalteparin 7500	10 000	Blind	Preop. 1 h	n.a.	> 5	FUT + veno.	30 days	43†
Koller *et al.*[51,52]	1986	Abdominal	n.a.	Dalteparin 2500	10 000	Blind	Preop. 1 h	n.a.	> 5	FUT + veno.	30 days	150
EFS[53,54]	1988	Abdominal	37‡	Nadroparin 2850	15 000	Open	Preop. 2 h	General	7	FUT + veno.	1 month	1 909
Fricker *et al.*[55]	1988	Abdominopelvic	100	Dalteparin 5000	15 000	Open	Preop. 2 h	n.a.	10	FUT + veno.	1–2 months	80
Bergqvist *et al.*[56,57]	1988–1990	Abdominal	63	Dalteparin 5000	10 000	Blind	Preop. 12 h	General or regional	5–8	FUT + veno.	1 month	1 002†
Caen[58]	1988	Abdominal	29	Dalteparin 2500	10 000	Blind	Preop. 2 h	General	7	FUT	1 month	385†
Borstad *et al.*[59]	1988	Gynaecological	n.a.	Dalteparin 5000	10 000	Blind	Preop. 1 h	n.a.	7	IPG + veno.	n.a.	215
Samama *et al.*[60–64]	1988–1994	General	n.a.	Enoxaparin 2000	15 000	Open	Preop. 2 h	General	7	FUT + veno.	7 days	335
Samama *et al.*[60–64]	1988–1994	General	n.a.	Enoxaparin 4000	15 000	Open	Preop. 2 h	General	7	FUT + veno.	7 days	250
Samama *et al.*[60–64]	1988–1994	General	n.a.	Enoxaparin 6000	15 000	Open	Preop. 2 h	General	7	FUT + veno.	7 days	307
Welzel *et al.*[65]	1988	Abdominal	n.a.	Certoparin 2500 + DHE	10 000 + DHE	Open	Preop. 2 h	n.a.	7	FUT	7 days	201†
Briel *et al.*[66]	1988	Gynaecological	n.a.	Dalteparin 5000	10 000 + DHE	n.a.	Preop.	n.a.	8	Thermography + veno.	n.a.	193†
Catania and Salanitri[67]	1988	Abdominal	46	Parnaparin 3200	15 000	Open	Preop. 2 h	General	7	n.a.	n.a.	173
Salcuni *et al.*[68]	1988	Abdominal	52	Parnaparin 3200	15 000	Open	Preop. 2 h	General	7	n.a.	n.a.	141
Kakkar *et al.*[69]	1989	Abdominal	48	Certoparin 3000 + DHE	10 000 + DHE	Blind	Preop. 2 h	n.a.	7–10	FUT + veno.	n.a.	179†
Adolf *et al.*[70]	1989	Abdominal	n.a.	Certoparin 3000	15 000	Blind	Preop. 2 h	n.a.	7–10	FUT + veno.	1 month	410
Heilmann *et al.*[71]	1989	Gynaecological	n.a.	Certoparin 3000	15 000	Blind	Preop. 2 h	General	7	IPG + veno.	10 days	300
Baumgartner *et al.*[72]	1989	Abdominal	16	Certoparin 3000 + DHE	5 000 + DHE	Blind	Preop. 2 h	n.a.	6–10	FUT + veno.	10 days	201
Dahan *et al.*[73]	1989	Thoracic	100	Nadroparin 2850	15 000	Open	Preop. 12 h	n.a.	7	FUT + veno.	n.a.	87†
Verardi *et al.*[74]	1989	Abdominal/ urological	n.a.	Parnaparin 6400	10 000	n.a.	Preop. 2 h	n.a.	7	FUT	n.a.	88
Creperio *et al.*[75]	1990	General	35	Dalteparin 2500	10 000	Blind	Preop. 2 h	General	5	FUT + veno.	n.a.	40
Hartl *et al.*[76]	1990	Abdominal	n.a.	Dalteparin 2500	10 000	Blind	Preop. 2 h	n.a.	7	FUT + veno.	> 7 days	250
Hoffmann and Largiader[77]	1990	Abdominal	n.a.	Certoparin 3000 + DHE	10 000	n.a.	Preop. 2 h	n.a.	n.a.	n.a.	n.a.	916

Table 3 Continued

Reference	Year	Type of surgery	Cancer surgery (%)	LMWH and dose (anti-Xa units)	UFH (units)	Study design	Time of first administration	Type of anaesthesia	Treatment duration (days)	Diagnosis of DVT*	Follow-up duration	Patients randomized
Koppenhagen *et al.*[78]	1990	Abdominal	38	Certoparin 3000	15 000	Blind	Preop. 2 h	General	8	FUT + veno.	7–10 days	104
Barbui *et al.*[79]	1990	General	n.a.	Nadroparin 2850	10 000	Open	n.a.	n.a.	7	FUT + veno.	n.a.	344
Leizorovicz *et al.*[80]	1991	Abdomino-thoracic and gynaecological	n.a.	Tinzaparin 2500 and 3500	10 000	Blind	Preop. 2 h	n.a.	7–10	FUT + veno.	1 month	1 290
Schielke *et al.*[81]	1991	Abdominal	n.a.	Certoparin 3000 + DHE	10 000 + DHE	Open	Preop. 2 h	n.a.	7–10	n.a.	7–10 days	98
Kaaja *et al.*[82]	1992	Gynaecological	18	Enoxaparin 2000	10 000	Blind	Preop. 2 h	General	3	n.a.	1 month	68
Koppenhagen *et al.*[83]	1992	Abdominal	57	Certoparin 3000	15 000	Blind	Preop. 2 h	General	7–10	FUT + veno	3 weeks	673
Borstad *et al.*[84]	1992	Gynaecological	n.a.	Dalteparin 2500	10 000	Blind	Preop. 1 h	n.a.	7	n.a.	n.a.	152
Hoffmann and Largiader[85]	1992	Abdomino-thoracic	n.a.	Certoparin 3000	10 000	Blind	Preop. 2 h	n.a.	> 7	n.a.	n.a.	594
Garcea *et al.*[86]	1992	Abdominal	48	Parnaparin 3200	15 000	Open	Preop. 2 h	n.a.	7	FUT	n.a.	90
Kakkar *et al.*[87–89]	1993–1997	General and gynaecological	41	Reviparin 1750	10 000	Blind	Preop. 2 h	n.a.	> 5	FUT + veno.	n.a.	1 351
Kakkar *et al.*[90]	1993	Abdominal	38	Dalteparin 2500	10 000	Blind	Preop. 1–4 h	General	5–10	n.a.	4–8 weeks	3 809†
Godwin *et al.*[91]	1993	Abdomino-pelvic	100	Ardeparin 90 and 50 units/kg b.i.d	10 000	Blind	Preop. 2 h	General or regional	n.a.	IPG, US + veno	n.a.	904
Gazzaniga *et al.*[92] (ISG)	1993	General and vascular	n.a.	Enoxaparin 2000	10 000	Open	Preop. 2 h	General	7–10	(D or US or IPG) ± veno.	6 weeks	1 122
Limmer *et al.*[93]	1994	General	n.a.	Antixarin 2500	15 000	Open	Preop. 2 h	General	8	FUT + veno.	8 days	203†
Eurin[94]	1994	Abdomino-pelvic	n.a.	Nadroparin 2850	15 000	Open	Postop. 2 h	Regional	7	(D + IPG or US) + veno.	7 days	480
Nurmohamed *et al.*[95]	1995	General	36	Enoxaparin 2000	15 000	Blind	Preop. 2 h	General	10	FUT + veno.	10 days	1 471
McLeod *et al.*[96–98] (Canadian)	1995–1997	Colorectal	n.a.	Enoxaparin 4000	15 000	Blind	Preop. 2 h	General	5–9	Veno.	5–9 days	1 349
Gonzalez *et al.*[99]	1996	Abdominal	n.a.	Bemiparin 2500	10 000	Blind	Preop. 2 h	General	7	(D or IPG) + veno	n.a.	166†
ENOXACAN[100]	1997	Abdomino-pelvic	100	Enoxaparin 4000	15 000	Blind	Preop. 2 h	General	8–12	Veno.	3 months	1 115
Heilmann *et al.*[101,102]	1997 1998	Gynaecological and breast	100	Certoparin 3000	15 000	Blind	Preop. 2 h	General	7	IPG + veno.	10 days	358
Haas *et al.*[103]	1999	General (84%)	26	Certoparin 3000	15 000	Blind	n.a.	n.a.	> 5	n.a.	14 days	23 078

*At end of the treatment. †No. of patients for whom the group distribution was available. ‡stratum of patients with cancer; LMWH, low molecular weight heparin; UFH, unfractionated heparin; DVT, deep vein thrombosis; EFS, European Fraxiparin Study; ISG, Italian Study Group; b.i.d., twice daily; DHE, dihydroergotamine; n.a., data not available; preop., before operation; postop., after operation; FUT, fibrinogen uptake test; veno, DVT confirmed by venography; IPG, plethysmography; US, ultrasonography; D, Doppler; SSHA, semi-synthetic heparin analogue

Table 4 Low molecular weight heparin *versus* unfractionated heparin: incidence of all evaluation criteria in each treatment group

		Patients randomized		Asymptomatic DVT*		Clinical PE		Clinical thrombo-embolism		Death		Major haemorrhage		Total haemorrhage		Wound haematoma		Transfusion	
Reference	Year	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH
Schmitz-Huebner *et al.*[44]	1984	84	42	3/81	0/39	0	0	0	0	n.a.	n.a.	2	0	n.a.	n.a.	17	8	n.a.	n.a.
Törngren *et al.*[45]	1984	309	162	37/279	21/148	2	1	n.a.	n.a.	12	7	n.a.	n.a.	n.a.	n.a.	48	19	29	16
Kakkar and Murray[46]	1985	200	200	5/196	14/199	0	1	0	2	5	6	n.a.	n.a.	n.a.	n.a.	11	14	65	57
Bergqvist *et al.*[47]	1986	215	217	13/215	9/217	0	1	n.a.	n.a.	n.a.	n.a.	10	3	25	10	13	7	75	55
Onarheim *et al.*[48]	1986	25	27	1/25	0/27	0	0	n.a.	n.a.	0	0	1	1	1	2	0	1	n.a.	n.a.
Sasahara *et al.*[49]	1986	137	132	14/134	13/126	0	2	n.a.	n.a.	2	5	n.a.	n.a.	n.a.	n.a.	4	3	19	31
Voigt *et al.*[50]	1986	103	97	1/103	1/97	0	1	0	2	4	6	3	1	6	11	3	10	55	57
Koller *et al.*[51,52]	1986	23	20	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	0	6	2	11	2	7	2	5	1
Koller *et al.*[51,52]	1986	75	75	2/70	1/68	0	1	n.a.	n.a.	0	0	1	0	11	11	3	2	4	5
EFS[53,54]	1988	968	941	27/960	42/936	1	5	3	11	11	12	n.a.	n.a.	179	176	83	86	150	144
Fricker *et al.*[55]	1988	40	40	0/40	0/40	0	4	1	5	n.a.	n.a.	2	1	8	13	n.a.	n.a.	n.a.	n.a.
Bergqvist *et al.*[56,57]	1988–1990	505	497	28/505	41/497	0	5	n.a.	n.a.	10	10	n.a.	n.a.	30	15	25	10	223	215
Caen[58]	1988	195	190	6/195	7/190	0	1	n.a.	n.a.	2	3	0	1	4	4	4	3	11	8
Borstad *et al.*[59]	1988	105	110	0/105	0/110	0	0	0	0	n.a.	n.a.	1	1	61	55	26	15	n.a.	n.a.
Samama *et al.*[60–64]	1988–1994	168	167	6/159	12/158	0	0	1	0	1	0	1	1	4	8	1	4	74	61
Samama *et al.*[60–64]	1988–1994	127	123	3/106	3/110	0	0	0	2	1	0	1	0	12	17	10	15	54	54
Samama *et al.*[60–64]	1988–1994	160	147	4/137	5/133	0	1	1	2	2	0	1	1	19	19	15	16	81	71
Welzel *et al.*[65]	1988	98	103	4/98	14/103	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	6	4	n.a.	n.a.
Briel *et al.*[66]	1988	95	98	1/95	1/98	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	3	2	n.a.	n.a.
Catania and Salanitri[67]	1988	88	85	n.a.	n.a.	0	0	1	6	2	3	0	0	5	8	5	8	8	11
Salcuni *et al.*[68]	1988	73	68	n.a.	n.a.	1	2	5	11	n.a.	n.a.	6	5	11	14	5	8	25	32
Kakkar *et al.*[69]	1989	88	91	8/88	10/91	2	0	n.a.	n.a.	n.a.	n.a.	2	0	6	3	2	1	n.a.	n.a.
Adolf *et al.*[70]	1989	205	205	9/202	6/202	3	1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	14	19	63	48
Heilmann *et al.*[71]	1989	150	150	2/150	6/150	0	0	n.a.	n.a.	n.a.	n.a.	2	3	n.a.	n.a.	19	27	n.a.	n.a.
Baumgartner *et al.*[72]	1989	99	102	6/87	7/89	1	1	n.a.	n.a.	1	2	0	0	n.a.	n.a.	1	0	n.a.	n.a.
Dahan *et al.*[73]	1989	46	41	0/46	0/41	0	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	4	n.a.	n.a.
Verardi *et al.*[74]	1989	44	44	1/44	3/44	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1	2	n.a.	n.a.
Creperio *et al.*[75]	1990	20	20	5/20	3/20	0	0	0	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hartl *et al.*[76]	1990	126	124	5/112	5/115	1	1	n.a.	n.a.	6	4	2	3	4	4	1	1	2	9
Hoffmann and Largiader[77]	1990	464	452	n.a.	n.a.	1	0	n.a.	n.a.	n.a.	n.a.	12	12	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Koppenhagen *et al.*[78]	1990	51	53	4/51	7/53	n.a.	n.a.	2	0	0	0	0	0	0	0	0	0	20	16
Barbui *et al.*[79]	1990	171	173	2/27	2/33	0	2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	10	9	n.a.	n.a.
Leizorovicz *et al.*[80]	1991	861	429	23/861	7/429	5	2	n.a.	n.a.	20	9	22	14	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Schielke *et al.*[81]	1991	47	51	n.a.	n.a.	0	0	0	0	1	2	1	0	n.a.	n.a.	n.a.	n.a.	12	8
Kaaja *et al.*[82]	1992	37	31	n.a.	n.a.	0	0	0	0	n.a.	n.a.	0	6	11	20	11	14	n.a.	n.a.
Koppenhagen *et al.*[83]	1992	336	337	24/323	26/330	0	3	n.a.	n.a.	2	3	n.a.	n.a.	3	1	2	0	7	13
Borstad *et al.*[84]	1992	77	75	n.a.	n.a.	1	0	1	0	2	0	14	9	26	24	5	11	n.a.	n.a.
Hoffmann and Largiader[85]	1992	298	296	n.a.	n.a.	1	1	n.a.	n.a.	n.a.	n.a.	10	7	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Garcea *et al.*[86]	1992	45	45	0/45	1/40	0	0	n.a.	n.a.	n.a.	n.a.	0	5	0	7	0	1	n.a.	n.a.
Kakkar *et al.*[87–89]	1993–1997	672	679	30/648	28/663	1	3	n.a.	n.a.	3	5	4	13	55	80	29	52	79	87
Kakkar *et al.*[90]	1993	1 894	1 915	n.a.	n.a.	22	19	34	32	73	56	69	91	186	243	27	52	n.a.	n.a.
Godwin *et al.*[91]	1993	595	309	0/595	3/309	1	1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	56	21	n.a.	n.a.	n.a.	n.a

Table 4 Continued

		Patients randomized		Asymptomatic DVT*		Clinical PE		Clinical thrombo-embolism		Death		Major haemorrhage		Total haemorrhage		Wound haematoma		Transfusion	
Reference	Year	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH
Gazzaniga *et al.*[92] (ISG)	1993	561	561	2/561	5/561	3	4	4	5	3	9	1	2	29	34	n.a.	n.a.	n.a.	n.a.
Limmer *et al.*[93]	1994	103	100	3/103	3/100	0	0	0	0	0	0	0	0	n.a.	n.a.	7	5	n.a.	n.a.
Eurin[94]	1994	241	239	1/240	0/239		0	1	0	n.a.	n.a.	1	0	40	37	n.a.	n.a.	7	7
Nurmohamed *et al.*[95]	1995	737	734	42/718	25/709	1	1	1	3	4	6	11	18	111	135	n.a.	n.a.	71	81
McLeod *et al.*[96–98] (Canadian)	1995–1997	674	675	44/468	44/468	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	28	21	70	44	n.a.	n.a.	n.a.	n.a.
Gonzalez *et al.*[99]	1996	84	82	0/84	0/82	0	0	0	0	0	0	0	5	5	20	5	15	n.a.	n.a.
ENOXACAN[100]	1997	555	560	45/312	58/319	0	2	4	6	26	34	23	16	104	96	n.a.	n.a.	284	242
Heilmann *et al.*[101,102]	1997–1998	179	179	10/160	10/164	7	4	n.a.	n.a.	5	3	27	47	39	75	18	29	21	29
Haas *et al.*[103]	1999	11 542	11 536	n.a.	n.a.	(17)	(19)	n.a.	n.a.	166	149	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total no. of studies†		51		41		45		23		30		36		32		38		25	
Total no. of patients†		48 624		17 995		46 646		13 776		41 387		18 555		19 315		16 087		12 777	

Values in parentheses are cases of fatal pulmonary embolism (PE). *Denominator is number of patients who had a systematic detection test for asymptomatic deep vein thrombosis (DVT) at the end of the treatment period. †Combined total numbers for low molecular weight heparin (LMWH) and unfractionated heparin (UFH) groups. EFS, European Fraxiparin Study; ISG, Italian Study Group; n.a., Data not available

Table 5 Meta-analysis (logarithm of relative risk method) of efficacy and safety criteria comparing low molecular weight heparin* with unfractionated heparin

	Relative risk	P	No. of studies	No. of patients
Asymptomatic DVT				
Nadroparin	0·61 (0·41–0·92)	0·02	5	2917
Certoparin	0·86 (0·65–1·14)	0·29	11	2921
Dalteparin	0·90 (0·65–1·26)	0·55	10	2764
Enoxaparin	0·96 (0·77–1·19)	0·70	7	4919
Parnaparin	0·33 (0·05–2·08)	0·24	2	173
Clinical thromboembolism				
Parnaparin	0·37 (0·15–0·88)	0·02	2	314
Nadroparin	0·32 (0·10–0·99)	0·05	3	2789
Enoxaparin	0·65 (0·31–1·36)	0·25	7	4668
Dalteparin	1·00 (0·63–1·58)	0·99	5	4296
Certoparin	0·87 (0·08–9·03)	0·91	4	1340
Major haemorrhage				
Certoparin	0·78 (0·56–1·08)	0·13	10	3076
Dalteparin	0·94 (0·72–1·22)	0·64	10	5568
Enoxaparin	1·09 (0·77–1·54)	0·63	8	6017
Parnaparin	0·89 (0·31–2·54)	0·82	3	404
Wound haematoma				
Certoparin	0·76 (0·58–0·99)	0·048	11	3021
Parnaparin	0·58 (0·29–1·16)	0·12	4	492
Nadroparin	0·92 (0·71–1·19)	0·54	4	2740
Enoxaparin	0·90 (0·49–1·65)	0·72	4	960
Dalteparin	1·24 (0·76–2·04)	0·39	11	6683

Values in parentheses are 95 per cent confidence intervals. *For each criteria, only low molecular weight heparin with two or more clinical trials are presented. DVT, deep vein thrombosis

Table 6 Incidence of all evaluation criteria in the unfractionated heparin group according to type of surgery

	Cancer surgery (%)	Non-cancer surgery (%)
DVT detected systematically at the end of the treatment period	6·0(0·6)	4·8(0·2)
Clinical PE	0·8(0·0)	0·4(0·0)
Clinical thromboembolism	1·8(0·5)	1·2(0·1)
Death	4·8(0·8)	1·5(0·1)
Major haemorrhage	8·1(1·0)	2·7(0·2)
Total haemorrhage	16·0(1·0)	12·0(0·4)
Wound haematoma	13·8(2·2)	5·9(0·3)
Transfusion	36·7(1·8)	19·3(0·5)

Values are adjusted incidences(S.D.). DVT, deep vein thrombosis; PE, pulmonary embolism

(RR 0·88 (0·64–1·20); P = 0·41). However, the risk of clinical VTE was significantly reduced by LMWH (RR 0·71 (0·51–0·99); P = 0·049) (*Fig. 2*). No reduction in death rate was observed (RR 1·04 (0·89–1·20)).

The incidences of major haemorrhage and wound haematoma in the UFH group were 3·2(0·2) and 6·1(0·3)

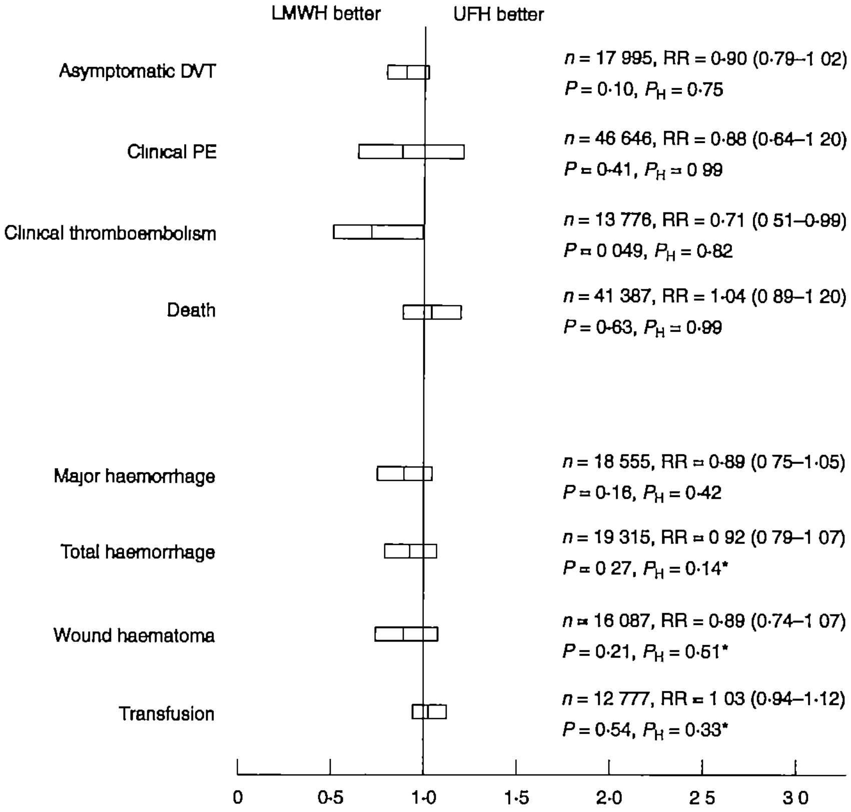

Fig. 2 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH). The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than UFH. If the value of 1 is included in the box, the result is not significant ($P > 0·05$). P_H indicates the result of the heterogeneity test. *A random model for the RR method had to be used because the heterogeneity test was positive, without any clear explanation for this heterogeneity between studies. DVT, deep vein thrombosis; PE, pulmonary embolism

per cent respectively. There was a reduction in the risk of major haemorrhage, total haemorrhage and wound haematoma in the LMWH group, but this trend did not reach statistical significance (*Fig. 2*).

Table 5 presents the results of this meta-analysis according to the different LMWHs involved. Only criteria for which the overall meta-analysis showed statistical significance or a trend towards statistical significance are displayed.

Sensitivity analyses

The meta-analysis results were not modified when dihydroergotamine treatment was taken into account and did not vary with UFH dose regimen (5000 units twice or three times daily) (data not shown).

Low molecular weight heparin *versus* unfractionated heparin in double-blind studies

When only the well identified double-blind studies were considered, the trends observed in favour of LMWH in the meta-analysis of all studies disappeared, not only for efficacy but also for safety criteria (*Fig. 3*).

Low molecular weight heparin *versus* unfractionated heparin in cancer surgery

The incidences of efficacy and safety criteria were higher in patients undergoing cancer surgery than in other patients (*Table 6*). However, the efficacy and safety of LMWH relative to UFH were similar in patients with cancer to those in patients without malignant disease (*Fig. 4*).

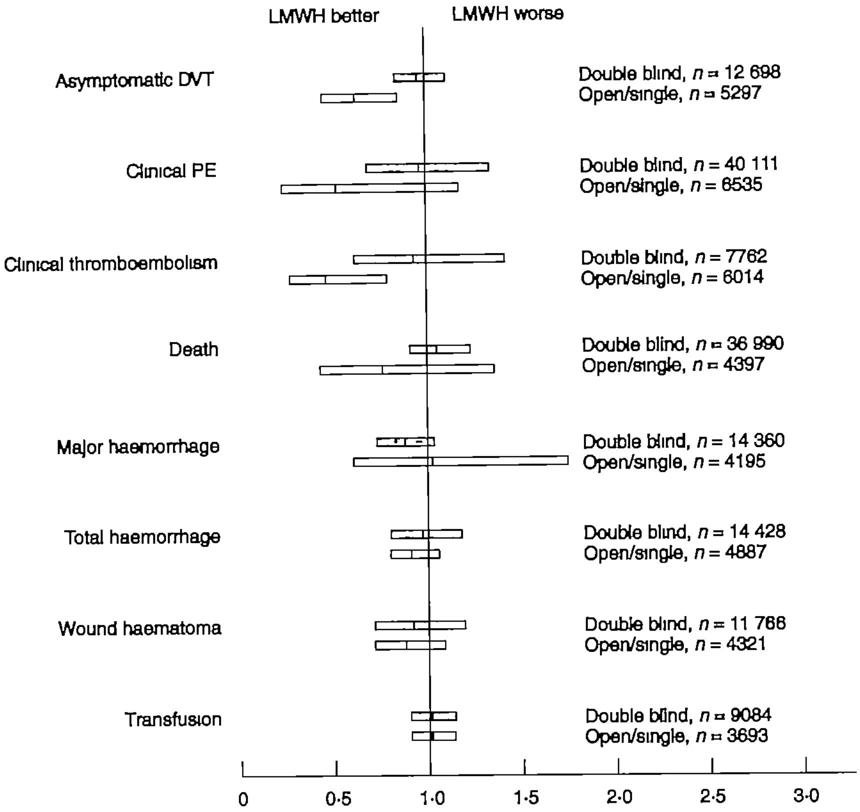

Fig. 3 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH) according to study design. If not specified, the study was considered as open. The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than UFH. If the value of 1 is included in the box, the result is not significant ($P > 0·05$). DVT, deep vein thrombosis; PE, pulmonary embolism

Low and high prophylactic dose regimens of low molecular weight heparin *versus* unfractionated heparin

Compared with UFH, low-dose LMWH (3400 anti-Xa units or less) did not significantly reduce the risk of VTE irrespective of the criteria used (systematically detected DVT at the end of the treatment period, clinical PE or clinical VTE) (*Fig. 5*). However, while achieving similar efficacy as UFH, low-dose LMWH was associated with a significant reduction in haemorrhagic risk, in particular that of major haemorrhage (RR 0·76 (0·63–0·92); $P = 0·005$) (*Fig. 5*).

Conversely, high-dose LMWH (more than 3400 anti-Xa units) appeared to be more effective than UFH, particularly with regard to clinical PE which was significantly reduced in the LMWH group (RR 0·18 (0·04–0·89); $P = 0·035$). This better efficacy was counterbalanced by a significant increase in the risk of haemorrhage, in particular that of major haemorrhage (RR 1·53 (1·07–2·19); $P = 0·02$) (*Fig. 5*). Although the number of studies was small, similar findings were obtained in patients undergoing cancer surgery (data not shown).

Discussion

In the absence of prophylactic treatment, the incidence of DVT when checked systematically on the tenth day after surgery was found to be approximately 15 per cent, with a risk of PE close to 0·5 per cent. This incidence is lower than that generally accepted in various consensus statements[1,2,104]. Patients undergoing general surgery therefore present an inherent risk of DVT similar to that of internal medicine patients[6] and patients with acute myocardial infarction[105], but less than that of those having orthopaedic surgery[1,2,4,5] or experiencing stroke[8].

This meta-analysis shows that treatment with LMWH at prophylactic doses provides a 72 per cent reduction in the

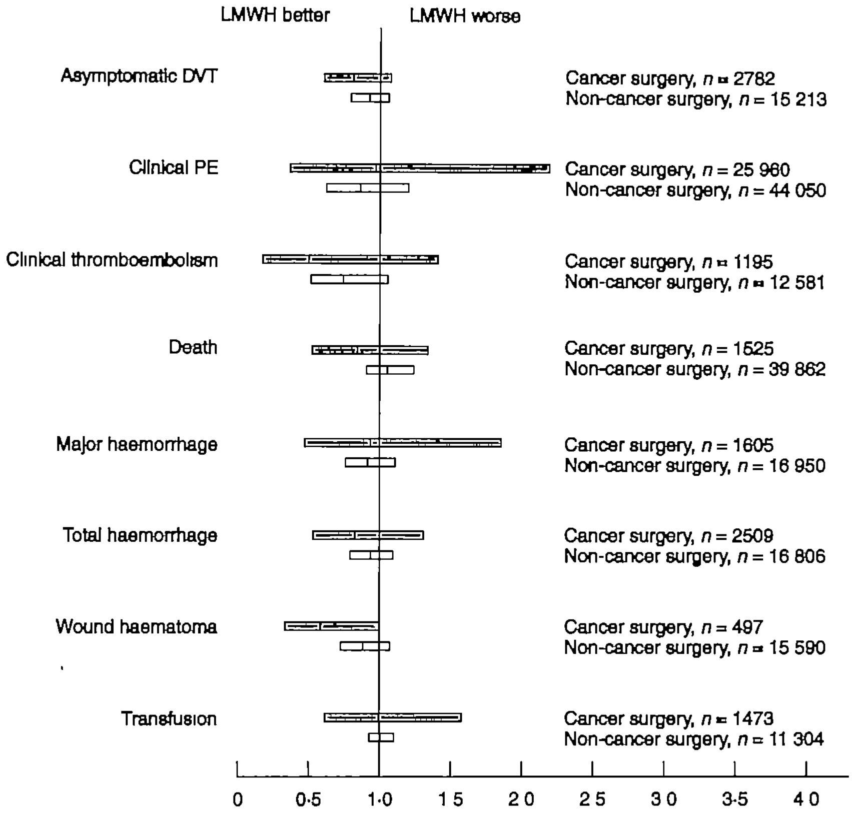

Fig. 4 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH) according to type of surgery. If not specified, the study was considered as non-cancer surgery. The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than UFH. If the value of 1 is included in the box, the result is not significant ($P > 0.05$). DVT, deep vein thrombosis; PE, pulmonary embolism

risk of DVT checked systematically at the end of treatment, compared with placebo or no treatment. This result is consistent with those reported in the meta-analyses conducted for other indications. Indeed, whether in internal medicine[6], orthopaedic surgery[4,5], stroke[8] or myocardial infarction[105], a constant reduction of 60–70 per cent of the risk of DVT is achieved by UFH or LMWH relative to placebo or no treatment, despite the different intrinsic risks of DVT in these situations in the absence of prophylaxis.

This 72 per cent reduction is associated with similar reductions of 75 per cent in clinical PE and 71 per cent in clinical VTE. This meta-analysis therefore appears to validate the evaluation criterion of 'asymptomatic DVT' as a surrogate endpoint for clinically important postoperative VTE. Despite an increase in major haemorrhage, the observed prophylactic effect of LMWH on VTE also seems to be associated with a non-significant reduction of 46 per cent in overall mortality rate (RR 0·54). The failure of the difference in this criterion to reach statistical significance seems to be a problem of statistical power; only 5142 patients were evaluated on this criterion. To show a significant reduction of 50 per cent in overall mortality, a total of 8000 patients per group would have been necessary (with $\alpha = 5$ per cent and $\beta = 10$ per cent).

With regard to the evaluation of haemorrhagic events, the criterion of wound haematoma could be proposed as a surrogate endpoint for major haemorrhage. Indeed, wound haematomas occur more frequently than major haemorrhages (10·3 *versus* 2·8 per cent) and the increase in frequency of both events under heparin treatment is comparable; RR of 1·88 for wound haematoma and of 2·03 for major haemorrhage.

As the reference treatment for VTE prophylaxis in general surgery in the 1980s was UFH[7], it was of interest to evaluate the effect of LMWH relative to UFH. This meta-analysis indicates that LMWH is at least as effective and safe

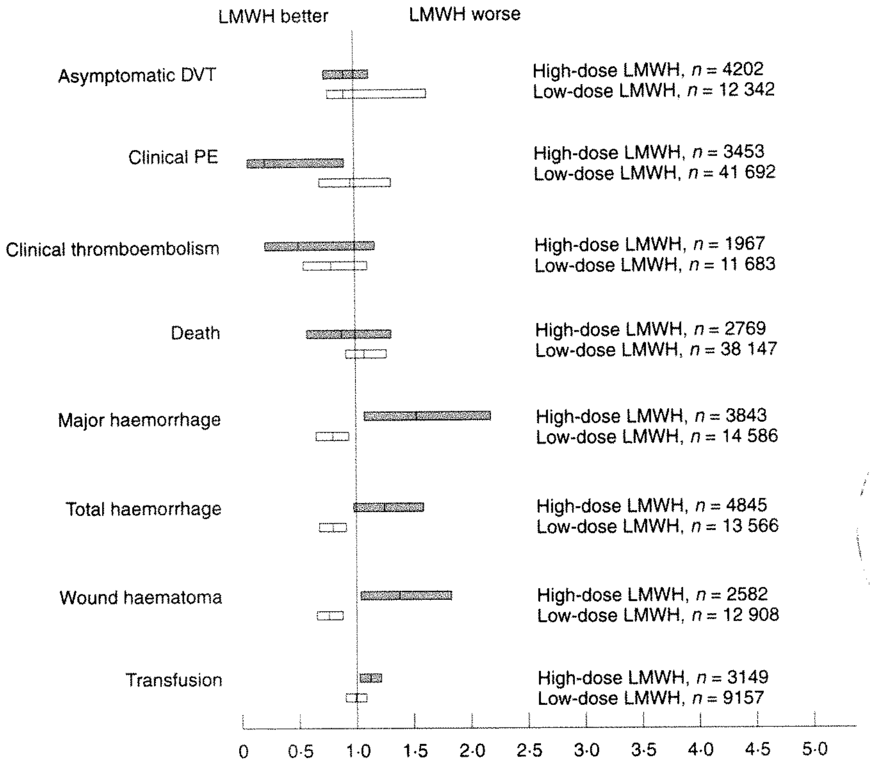

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Fig. 5 Meta-analysis (logarithm of relative risk (RR) method) of efficacy and safety criteria comparing low molecular weight heparin (LMWH) with unfractionated heparin (UFH) according to LMWH dose regimen (low dose, 3400 anti-Xa units or less; high dose, more than 3400 anti-Xa units). If the dosage in anti-Xa units was not available, the study was considered as missing. The RR for each criterion is shown as a vertical line within a box, which represents the 95 per cent confidence interval. A RR of less than 1 indicates that LMWH is more effective than UFH. If the value of 1 is included in the box, the result is not significant ($P > 0{\cdot}05$). DVT, deep vein thrombosis; PE, pulmonary embolism

as UFH, in terms of VTE reduction and haemorrhagic events (RR 1 or less for all criteria). These results are not modified by the level of risk associated with the type of surgery, i.e. cancer surgery *versus* non-cancer surgery. The observed trend in favour of LMWH should be viewed with caution since, when only double-blind studies are taken into account, the results show a close similarity of LMWH and UFH with regard to both thromboembolic and haemorrhagic events. These results are in agreement with those published by Koch *et al.*[11] in 1997, with respect to asymptomatic DVT and wound haematoma; they update this previous meta-analysis with eight additional double-blind studies and more than 25 000 additional patients. In addition, similar findings were observed for clinical end-points. However, even if LMWH is merely as effective as UFH in the prophylaxis of VTE, the former is now the reference treatment for reasons of ease of use.

LMWHs differ to some extent in their pharmacokinetic and anticoagulant profiles, and results obtained with one LMWH may not be simply extrapolated to another since treatment regimens differ somewhat between drugs[106,107]. The present results support this, as nadroparin and parnaparin showed better efficacy than UFH when considering asymptomatic DVT and clinical thromboembolism, whereas there were fewer wound haematomas with certoparin than with UFH (*Table 5*). However, these results should be interpreted cautiously in the absence of any direct comparison between LMWHs.

For general surgery, which involves only moderate thrombotic risk in comparison to orthopaedic surgery, the use of low prophylactic doses of LMWH (3400 anti-Xa units or less) seems to be as effective and safer than UFH. In contrast, high doses of LMWH (more than 3400 anti-Xa units) appear to be more effective, but less safe than UFH. This threshold of 3400 anti-Xa units has already been suggested[1,10,11] and permits a distinction between the low-dose and high-dose prophylactic regimens proposed by the pharmaceutical firms manufacturing the various LMWHs currently available. Three studies provide a direct comparison between low and high doses of LMWH[25,27,29].

However, only the study reported by Bergqvist *et al.*[29] had sufficient statistical power (2097 patients) to show that the high-dose LMWH reduces the incidence of asymptomatic DVT by 50 per cent compared with low-dose LMWH, but at the cost of a fourfold greater risk of major haemorrhage. In view of the paucity of data providing any direct comparison of different doses, it remains difficult to say which dosage regimen of LMWH, high or low, yields the better risk : benefit ratio in general surgery and, in particular, in cancer surgery.

In conclusion, asymptomatic DVT may be regarded as a reliable surrogate endpoint for clinical outcomes in studies investigating thromboprophylaxis in general surgery. LMWH is at least as effective and as safe as UFH. Determination of the optimal dose regimen of LMWH in general surgery requires further investigation.

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Prospective randomized trial of polypropylene mesh compared with nylon darn in inguinal hernia repair

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Background: The main aim of this study was to evaluate outcome in patients undergoing open inguinal hernia repair with either polypropylene mesh or nylon darn.

Methods: This was a randomized prospective trial of patients who underwent the procedure with follow-up at 1 week, 6 weeks and 1 year.

Results: One hundred men underwent 105 repairs by consultant surgeons and registrars; there were 54 mesh and 51 nylon repairs. Demographics in both groups were similar at the start of the trial, as were the types of hernia. The pain scores at 24, 48 and 72 h were similar, as was the duration of analgesia requirement. There were no differences in early or late complications. Return to normal activity in each group was also similar, with a mean time of 5 weeks. The recurrence rate in both groups was comparable: 4 per cent after mesh repair and 4 per cent after darn repair at 1-year review.

Conclusion: Open inguinal hernia repair with a nylon darn was equivalent to polypropylene mesh with respect to early measures of postoperative outcome and recurrence at 1 year.

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Introduction

There are many ways of repairing an inguinal hernia, with over 80 operative techniques described since 1887 when Bassini reported his method. Extensive clinical research has been undertaken to assess outcome following inguinal hernia repair[1]. High recurrence rates using fascia for inguinal hernia repair or suturing under tension prompted the development of minimal tension nylon darn, and then polypropylene mesh, to reinforce the posterior wall of the inguinal canal during hernia repair. A nylon darn, originally described by Moloney *et al.*[2], is a cheap and effective way of repairing a hernia. The recurrence rate reported from the original series was 0·8 per cent[3]. More recently the use of polypropylene mesh has become popular, largely because of excellent results reported by Lichtenstein *et al.*[4]. The recurrence rate with this procedure was reported as nil in Lichtenstein's personal series, but as around 1 per cent in other series.

As laparoscopic approaches to hernia repair are developed and evaluated, it is important to understand the most effective open approach. In a major study of open surgery *versus* laparoscopic hernia repair, the open arm contained many different techniques, the results of which could vary substantially[5]. A recent attempt to define the best open technique for hernia repair by analysing randomized trials was limited by the variability of the outcomes reported, with some trials quoted as having follow-up as short as 7 weeks; few trials have reported short-term complications, pain assessment and return to normal activities[6].

The aim of this study was to compare the two techniques commonly employed in the treatment of a primary inguinal hernia in men, assessing complications, pain, return to normal activities and early recurrence.

Patients and methods

This randomized prospective trial was conducted at Flinders Medical Centre. The inclusion criteria were: all men with a primary inguinal hernia, both surgeon and patient willing to participate, age 18–90 years, support available at home for postoperative care, American Society of Anesthesiologists grade 1 or 2 on a preoperative assessment, and a telephone available to the patient at home to call for medical assistance, if necessary. Patients with recurrent hernias and inguinoscrotal hernias were excluded.

The Committee on Clinical Investigation at Flinders Medical Centre approved the trial. Men who agreed to be in the trial were randomized to one of the two groups, to have the repair with either mesh or nylon darn. Randomization was done after consent by the patient using sealed envelopes. In patients with bilateral hernias the individual side was randomized.

All operations were performed by a consultant surgeon or registrar. A standard procedure was used. After initial dissection of the hernia, the transversalis fascia was plicated with 2/0 polypropylene if the posterior wall was weak, and any indirect sac was excised. The repair was then done using either the darn or mesh repair. The nylon darn method involved 1 nylon being placed from the conjoint tendon to the inguinal ligament, without tension, in an interwoven fashion. The mesh repair involved a polypropylene mesh being placed between the conjoint tendon and the inguinal ligament and secured with 2/0 polypropylene. The spermatic cord was then placed between the two tails of the mesh for creation of a new internal ring. An excellent description of both techniques has been given by Maddern *et al.*[7].

There was no restriction on the type of anaesthesia; local anaesthesia (20 ml 1 per cent lignocaine with adrenaline 1 : 200 000), spinal or general anaesthesia was employed depending on surgeon, patient and anaesthetic factors. All patients had 10 ml 0·25 per cent bupivacaine with adrenaline infiltrated around the ilioinguinal nerve, pubic tubercle and subcutaneously at the completion of the procedure.

Nursing staff from the day surgery unit recorded pain scores, either in hospital or by telephone at 24, 48 and 72 h after operation. Analgesic use was also recorded. Patients were then seen as outpatients at 1 and 6 weeks after operation by the treating medical staff (who were not blinded to the type of repair used) to check wound healing and any early complications.

The study commenced in 1994 and a review of the first 100 patients who had completed 1 year or more since the operation was conducted in 1998 by an independent consultant surgeon who did not know the nature of the operation. This surgeon collated the pain scores and length of analgesic use, corroborated reports of any complications, estimated the time of return to normal activities and examined the patients for recurrence.

There has been ongoing recruitment since that point to increase the power of the study with regard to the question of recurrence rates.

Pain scores were recorded at 24, 48 and 72 h and given a numerical value for statistical analysis: 1, none; 2, mild; 3, moderate; 4, severe; 5, unbearable. Complications were classified as early (within the first week) or late. Data were analysed for statistical significance with the χ^2 test, Fisher's exact test and t tests. $P < 0·05$ was considered significant.

Results

One hundred men were randomized with 105 hernias in total. Some 54 hernias were repaired with mesh and 51 with nylon. Ninety-five men had a unilateral hernia and five were bilateral (repaired simultaneously without increasing the length of hospital stay). Seven men were lost to follow-up because of change of address, change of phone number or death (five patients). Complete follow-up was obtained for 89 per cent of hernia repairs. Demographic characteristics were similar in both groups at the start of the trial.

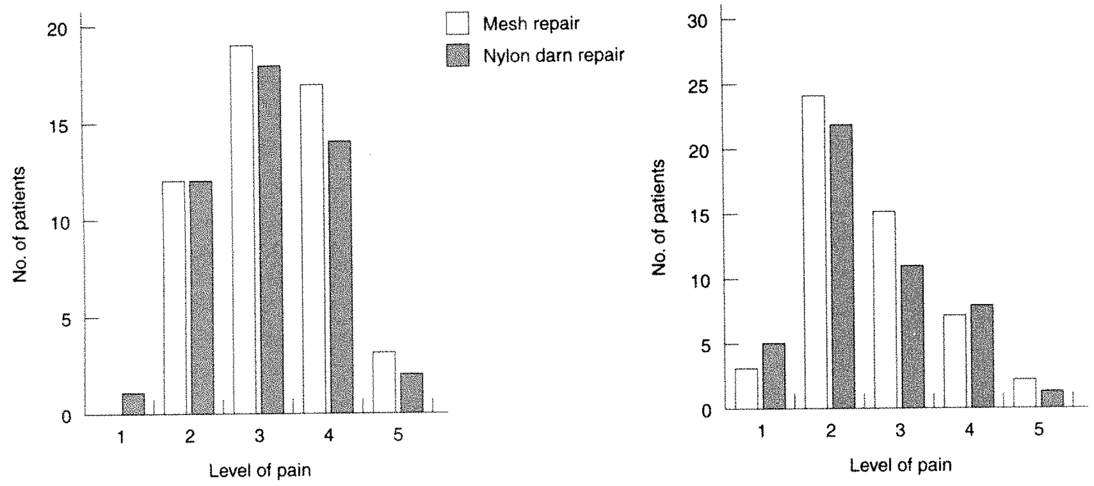
The mean(s.d.) age of patients in the mesh repair group was 53(19) (range 19–89) years, compared with 56(18) (range 18–87) years in the darn repair group. Twenty-five direct hernias were repaired with mesh and 28 direct hernias with nylon. Right-sided hernias predominated: 36 of 54 in the mesh group and 29 of 51 in the nylon group. The primary anaesthetic was local anaesthesia only in eight patients with mesh and in 11 with the nylon; spinal anaesthesia was used in seven patients with mesh and in six with nylon; and general anaesthesia was employed in 39 patients with mesh and in 34 with nylon. There was no relation between complications or postoperative recovery and the type of primary anaesthesia.

Pain scores

There were no significant differences in pain scores at 24, 48 and 72 h (*Fig. 1*). At 24 h the mean(s.d.) pain score for mesh repair was 3·22(0·88) and that for the nylon repair was 3·09(0·90) (t test for equality of means 0·72, P = 0·47, 95 per cent confidence interval (c.i.) of the mean – 0·23 to 0·49). At 48 h the mean pain score for the mesh repair was 2·92(0·89) and that for the nylon repair was 2·77(0·96) (P = 0·41, 95 per cent c.i. – 0·2.1 to 0·53). After 72 h the mean pain score for the mesh repair was 2·63(0·94) and that for the nylon repair was 2·53(0·97) (P = 0·62, 95 per cent c.i. – 0·29 to 0·48).

Analgesia requirement

Analgesic use was similar in both groups. Some form of analgesia was used by 81 per cent of patients after mesh repair and by 88 per cent following darn repair (χ^2 = 0·48, 1 d.f., P = 0·49) Patients in the mesh repair group required oral analgesia for a mean(s.d.) of 5·63(4·11) days, compared with 3·96(4·99) days in the darn group (t test for equality of means 0·13, P = 0·19, 95 per cent c.i. of the mean – 0·83 to 4·18).



a Pain scores at 24 h

b Pain scores at 72 h

Fig. 1 Pain scores after hernia repair with mesh or nylon darn at **a** 24 h and **b** 72 h. Pain score: 1, none; 2, mild; 3, moderate; 4, severe; 5, unbearable

Return to activity

The time taken for patients to get back to normal activity was identical in the two groups. The mean(s.d.) time after mesh repair was 5·13(3·67) weeks and that following nylon repair was 5·13(4·17) weeks (*t* test for equality of means −0·01, *P* = 0·99, 95 per cent c.i. of the mean −1·63 to 1·61).

Complications and recurrence

There was no statistically significant difference between the two groups in the rate of early complications (28 per cent after mesh repair *versus* 33 per cent after nylon repair; χ^2 = 0·23, 1 d.f., *P* = 0·63) or late complications (15 per cent after mesh repair *versus* 20 per cent after darn repair; χ^2 = 0·48, 1 d.f., *P* = 0·49) (*Table 1*).

Two hernias recurred after nylon repair (one at 2 years, one at 8 months). Both were lateral to the deep inguinal ring and were judged to be due to inadequate tightening of the ring at the time of re-repair. There were two recurrences after mesh repair: one at the medial end of the inguinal canal (the mesh was detached from this area), while the cause of the other is not known (patient operated on outside Flinders Medical Centre).

Table 1 Complications after hernia repair

	Mesh	Nylon darn
Early (≤ 7 days)		
Haematoma	7 of 53 (13)	7 of 49 (14)
Infection	2 of 53 (4)	1 of 49 (2)
Neuralgia	3 of 53 (6)	4 of 49 (8)
Seroma	1 of 53 (2)	2 of 49 (4)
Wound oozing	1 of 53 (2)	0 of 49 (0)
Urinary retention	3 of 53 (6)	4 of 49 (8)
Late (> 7 days)		
Neuralgia	4 of 48 (8)	7 of 45 (16)
Scar tenderness	2 of 48 (4)	0 of 45 (0)
Recurrence	2 of 54 (4)	2 of 51 (4)

Values in parentheses are percentages

Discussion

Results of this trial to date indicate that polypropylene mesh repair has no added advantage over nylon darn with respect to early postoperative pain, complications or return to normal activities. Furthermore, the rate of early recurrence was identical. These findings contrast with previous randomized studies that suggest open mesh repair causes less postoperative pain[4] and results in a quicker return to normal activity[8]. That mesh repairs are associated with fewer postoperative complications and a lower recurrence rate has not been supported by the results of this trial to date. As mesh is more expensive and, if it becomes infected (albeit rarely), may require removal, the results of this study question its widespread application. The results emphasize the importance of independent assessment of the patient with respect to pain scores and duration of analgesia, return to normal activities and recurrence.

The length of time to full recovery in this trial was an average of 5 weeks and was identical for hernias repaired with mesh or nylon. The purported advantage of mesh in a more rapid recovery was not supported by this trial in which independent data were collected. This recovery time is 1–2 weeks longer than in recent series[5,9,10]. The patients in the present study were generally older and had a higher rate of analgesic consumption, perhaps highlighting that different patient populations may attend different centres.

It has been advised that all centres, particularly training institutions, use mesh because recurrence rates are lower[11]. The present results indicate that this is not the case for early recurrence, thus emphasizing the importance of training and supervision, no matter which technique is employed. In a randomized trial of Shouldice repair compared with nylon darn, recurrence rates were similar: 4 per cent for the Shouldice method and 1·8 per cent for the darn[12]. Moreover, the recurrence rate for the Shouldice method was higher in this general surgical practice than the 1·1 per cent reported from the Shouldice Clinic[13].

Long-term follow-up is required for full determination of recurrence rates. It has been suggested that a minimum of 10 years is needed as 20 per cent of recurrences will not be apparent for 15 years[14]. It is difficult to organize a trial over that length of time. Early recurrence is likely to represent technical failure. The recurrence rate in the present study of 4 per cent, with two after each technique, is slightly higher but fairly comparable to the findings of similar studies at 12 months after operation. In a study with a large number of patients[5] the recurrence rate at 12 months was 3 per cent, and in a recent analysis[6] the hernia recurrence rate in non-mesh repairs was 4·4 per cent and that in mesh repairs 1·4 per cent.

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Provocation of experimental aortic inflammation and dilatation by inflammatory mediators and *Chlamydia pneumoniae*

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Background: The macrophage appears to have a key role in the inflammation and proteolysis associated with the growth and development of abdominal aortic aneurysms. The role of inflammatory mediators and *Chlamydia pneumoniae* in stimulating the influx of macrophages and dilatation of the abdominal aorta was investigated in an experimental model.

Methods: Periaortic application of calcium chloride solution (and monocyte chemoattractant protein (MCP) 1, a cocktail of cytokines or *C. pneumoniae*) to the abdominal aorta of New Zealand White rabbits was performed at laparotomy. Some animals were fed a cholesterol-rich diet. The diameter of the aorta was measured by ultrasonography and after perfusion fixation, 3 weeks after laparotomy. Aortic sections were stained with RAM-11 to identify macrophages for counting. The presence of *C. pneumoniae* DNA was confirmed using the polymerase chain reaction.

Results: Aortic macrophage influx in response to MCP-1, thioglycollate or *C. pneumoniae* was more than doubled in the cholesterol-fed animals. In response to human recombinant MCP-1 (1 μg) the mean(s.d.) macrophage count increased from 79(19) to 340(215) per unit area ($P < 0·02$). Even in cholesterol-fed animals, application of MCP-1 (recombinant human or rabbit form) was not associated with aortic dilatation. Application of thioglycollate 0·1 mol/l, or live or formalin-inactivated *C. pneumoniae* ($0·5 \times 10^8$ organisms), was associated with a similar increase in macrophages to that caused by MCP-1 and a significant (approximately twofold) increase in aortic diameter after 3 weeks.

Conclusion: Macrophage influx into rabbit abdominal aorta, without macrophage activation, is insufficient to cause experimental aortic dilatation. *C. pneumoniae* antigens appeared to stimulate aortic dilatation, probably by specific activation of macrophages.

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Introduction

Proteolysis and inflammation is the emerging paradigm for the pathological mechanism underlying the development of abdominal aortic aneurysm[1]. Inflammatory cells probably enter the aortic wall through the vasa vasorum of the adventitia and are found throughout the wall, but with particular concentration at the media–adventitia borders and in the adventitia[2–4]. The inflammation appears to be chronic in nature with mixtures of lymphocytes and macrophages[2–4]. The macrophage appears to be a particularly important cell, being a source of inflammatory cytokines, prostanoids and metalloproteinases[5,6].

In humans there is only the opportunity to study end-stage disease, in the form of biopsies of the aneurysm wall. This has been rewarding in providing details of the chronic inflammatory infiltrate and indicating the relationship between adventitial inflammation and aneurysm diameter[2–4]. However, there is little opportunity to investigate the dynamics of macrophage trafficking and whether inflammation is a cause of, or a reaction to, aneurysm disease. Such investigations are more readily accomplished in animal models. A common experimental model of aortic aneurysm results from the intra-aortic infusion of pancreatic elastase in rats[7]. In this model there is synchronous aortic dilatation, macrophage influx and an increase in proteolytic enzyme activity[7,8]. An alternative experimental model results from the periaortic application of calcium chloride solution in rabbits[9]. Again, experimental dilatation is associated with macrophage influx[9].

Macrophage recruitment is facilitated by a number of discrete proteins, of which monocyte chemoattractant protein (MCP)-1 is the most potent chemoattractant. Different chemoattractants stimulate the recruitment of neutrophils and lymphocytes. Macrophage recruitment also occurs in response to chronic infection. There is evidence to support current or previous infection with *Chlamydia pneumoniae* in about half of all aneurysm biopsies[10,11]. Through infection or antigenic responses, this organism also may elicit macrophage recruitment.

The purpose of this study was to investigate the relationship between macrophage recruitment into the aortic wall and experimental aortic dilatation.

Materials and methods

New Zealand White rabbits (2·2–3·5 kg) were subjected to laparotomy in accordance with approved protocols (PIL70/4221). The rabbits were fed either standard chow or a cholesterol-enriched diet (Stanrab plus 1 per cent cholesterol; Lillico, Betchworth, UK) starting 2 days before operation. Initially all rabbits were seronegative for chlamydial antigens. Anaesthesia was obtained using a combination of intramuscular fentanyl (Hypnorm; Roche, Welwyn Garden City, UK) and intravenous midazolam (Hypnovel; Roche, Welwyn Garden City, UK), with oxygen at 2 l/min delivered by facial mask. Before laparotomy, the diameter of the abdominal aorta (mean of three readings) was measured by ultrasonography (limits of agreement ± 0·2 mm)[9]. The abdomen was opened through a midline incision and the infrarenal aorta dissected, taking care not to damage any lumbar vessels. Calcium chloride 0·2 mol/l solution was applied at a slightly lower concentration than described previously[9], to avoid excessive aortic calcification. Cytokines were applied directly to the aortic wall using a sterile-tipped micropipette, after which the treated segment of aortic wall was wrapped in Seprafilm® (Genzyme, Haverhill, UK) to confine the cytokines to the aortic wall and prevent bowel adhering to the treated area. For experiments using Seprafilm®, the hyaluronan appeared to bind calcium and it was necessary to reduce the concentration of calcium chloride to 0·1 mol/l to avoid excessive calcification and ossification of the aorta. Recombinant human cytokines (MCP-1, tumour necrosis factor (TNF) α and interleukin (IL) 1β) were obtained from R & D Systems (Abingdon, UK). Recombinant rabbit MCP-1 was a gift from Dr T. Yoshimura (Kumamoto University, Kumamoto, Japan). *C. pneumoniae* was applied in calcium chloride solution (total volume 3·5–4·0 ml containing 0·5 × 10^8 organisms). The chlamydial preparations (live, formalin fixed and heat inactivated) were a gift from Dr B. Thomas (Imperial College at St Mary's, London, UK). Similarly sodium thioglycollate 0·1 mol/l was applied in 3·5–4·0 ml calcium choride solution. The abdomen was sutured by mass closure using 3/0 polypropylene, followed by subcuticular skin suture (3/0 polyglycolic acid). Three weeks later the diameter of the aorta was measured by ultrasonography, a blood sample was removed for the measurement of serum cholesterol, using a colorimetric enzyme assay kit (Boehringer, Lewes, UK), and the animals were killed. In some animals the aorta and other vessels were fixed by perfusion with 5 per cent glutaraldehyde at a pressure of 100 cmH_2O. Where the aorta was not perfusion fixed, a sample was frozen at –70°C for later extraction of DNA and the remainder was fixed in formalin.

All aortas were taken in cross-section and processed with haematoxylin and eosin and elastic van Gieson stains. Macrophages were identified using the antibody RAM-11 (Dako, Ely, UK) at 1/50 dilution. Histological analyses and macrophage counting were performed by one of two observers, who were blinded to the treatments applied to each specimen. For quantitative analysis, cells from consecutive, circumferential, non-overlapping aortic fields were examined under a digital image capturing light microscope and cell counting was performed using AnalySiS™ (UK) image analysis software (Soft Imaging Software, Münster, Germany). Aortic wall thickness (lumen to external elastic lamina) was measured in four quadrants and the mean calculated.

DNA was extracted from frozen, pulverized tissue using a commercial kit (Dneasy™; Qiagen, Crawley, UK). Amplification of the *omp-1* and β-actin genes was performed using 50–100 ng template DNA, in a 50-μl reaction mixture containing magnesium chloride 1·5–2·5 mmol/l, 2 units Taq polymerase (Promega, Southampton, UK), 10 pmol primers (Perkin-Elmer, Warrington, UK), 1 volume buffer 'B' (Promega, Southampton, UK) and deoxyribonucleoside 5′-triphosphates 200 μmol/l (Pierce and Warriner, Chester, UK). The β-actin primers (5′–3′) were ATCATGTTT-GAGACCTTCAACACCCC and CTTGATCTTCAT-TGTGCTGGGTGCCA. The first- and second-round primers (5′–3′) for amplification of the *omp-1* gene were GTTGTTCATGAAGGCCTACT, TGCATAACCTA-CGGTTT and TTTAGATCATGGTGTCATTCGC, AAGGTTCATCCTTGAAGGCA respectively. Cloned TWAR183 DNA was a gift from Dr N. Carey (Charing Cross Hospital, London, UK). The sensitivity of the nested *omp-1* gene amplification was 70 gene copies.

Most data were analysed using analysis of variance, with Fisher's exact significance for paired comparisons. Aortic diameters were compared with paired *t* tests. Values are reported as mean(s.d.).

Results

Two rabbits died from respiratory arrest before the peritoneal cavity was opened, but the remaining animals survived laparotomy. The median serum cholesterol concentration was 0·6 (range 0·3–1·5) and 78 (range 38–112) mmol/l for rabbits fed normal and cholesterol-enriched chow respectively. Animals fed cholesterol-enriched chow did not gain weight during the 3 weeks following laparotomy, whereas the animals fed normal chow gained 0·3(0·1) kg. Many of the cholesterol-fed rabbits developed arcus senilis rings in the iris and one developed jaundice. The maximum external aortic diameter measured by ultrasonography exceeded the internal diameter, measured on sections of perfusion-fixed aorta, by 0·5(0·1) mm.

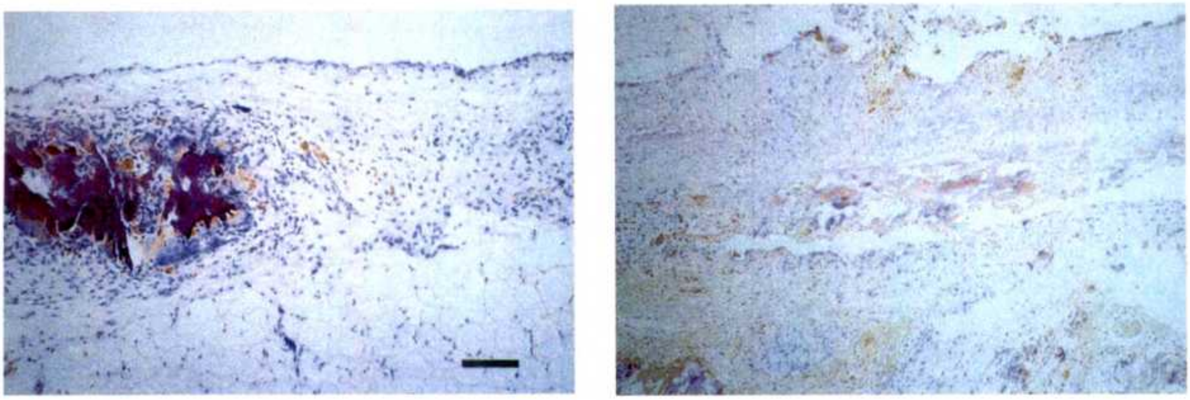
Aortic diameter and macrophage infiltration in rabbits fed normal chow

Application of rabbit or human MCP-1 (1 µg), thioglycollate 0·1 mol/l or *C. pneumoniae* resulted in a modest, but significant, increase in macrophage influx (*Table 1*). This influx was mainly into the aortic media, although some cells in the intima and adventitia also stained with RAM-11 (*Fig. 1a*). The application of any of these substances was not associated with a significant increase in aortic diameter or aortic wall thickness.

Table 1 Aortic diameters and macrophage infiltration in rabbits fed normal chow

		Mean aortic diameter (mm)		Mean macrophage count per unit area at 3 weeks
	n	Start	3 weeks	
Control	4	3·2(0·6)	3·5(0·5)	10(6)
Thioglycollate 0·1 mol/l	4	2·9(0·5)	3·5(0·4)	126(31)†
MCP-1				
Human 1 µg	4	3·4(0·5)	3·4(0·5)	79(19)†
Human 2 µg	2	3·0(0·0)	3·5(0·7)	40(23)
Rabbit 1 µg	4	3·0(0·3)	4·0(0·8)	66(33)†
Formalin-fixed *C. pneumoniae**	2	2·8(0·1)	3·0(0·1)	108(22)†

Values are mean(s.d.). All agents were added to 0·2 mol/l calcium chloride. *0·5 × 10^8 organisms. MCP, monocyte chemoattractant protein; *C. pneumoniae*, *Chlamydia pneumoniae*. †$P < 0.02$ *versus* no additive (analysis of variance)



a Normal chow **b** High-cholesterol diet

Fig. 1 Macrophage infiltration into the aortic wall. Sections have been stained with antibody to rabbit macrophages (RAM-11) and counterstained with haematoxylin. The scale bar represents 50 µm. **a** Aortic section from a rabbit fed normal chow 3 weeks after the periaortic application of calcium chloride and recombinant monocyte chemoattractant protein (1 µg). **b** Aortic section from a rabbit fed high-cholesterol diet 3 weeks after the periaortic application of calcium chloride containing 0·5 × 10^8 organisms of formalin-fixed *Chlamydia pneumoniae*. The aortic architecture is severely disrupted, with macrophage staining in the intima, media and adventitia

Aortic diameter and macrophage infiltration in rabbits fed cholesterol-enriched chow

In animals fed cholesterol-enriched chow the periaortic application of calcium chloride 0·2 mmol/l alone was sufficient to cause a marked influx of macrophages, localized around the medial calcification, but this treatment did not alter aortic diameter (*Table 2*). The macrophage count varied quite widely within each treatment group, but for every treatment the count was significantly higher in cholesterol-fed animals than in those fed normal chow (*Tables 1* and *2*) ($P < 0·05$). Addition of recombinant MCP-1 (1 μg of the human or rabbit form) had a similar effect to thioglycollate on the number of macrophages in the aortic wall, but did not appear to provoke an increase in aortic diameter (*Table 2*). The application of thioglycollate or *C. pneumoniae* (live or formalin fixed) in calcium chloride was associated with a significant (approximately twofold) increase in aortic diameter after 3 weeks, and a further increase in the number of infiltrating macrophages in the media (*Fig. 1b*, *Table 2*). These increases in aortic diameter were not associated with an increase in aortic wall thickness. In contrast, the application of heat-inactivated *C. pneumoniae* or a cytokine cocktail (MCP-1, TNF-α and IL-1β, 1 μg of each) was associated with minimal macrophage influx and minimal change in aortic diameter or wall thickness.

Detection of *Chlamydia pneumoniae* in dilated aortas

To ascertain whether chlamydial DNA was present in aortas treated with bacterial preparations, DNA was prepared from aortic samples and subjected to polymerase chain reaction (PCR) specific for β-actin and the chlamydial *omp-1* gene. All samples tested positive for β-actin. Of the four samples to which live preparations had been applied, two tested positive for the *omp-1* gene. Of the five samples to which formalin-fixed preparations had been applied, two tested positive for the *omp-1* gene. In all of the samples in which the *omp-1* gene was not amplified, there was evidence of the presence of significant PCR inhibitors, since no amplification was achieved after the sample had been spiked with cloned chlamydial DNA. In contrast, there was no evidence of significant PCR inhibition in DNA from the four aortas treated with heat-inactivated preparations. Although no unspiked samples of aortic DNA tested positive for the *omp-1* gene, some splenic DNA from these animals did test positive for the *omp-1* gene.

Discussion

The macrophage, with its ability to secrete proteases such as matrix metalloproteinase 9, has been considered to have a pivotal role in the pathogenesis of abdominal aortic aneurysm[1,3,5]. Hypercholesterolaemia is essential for the development of calcium chloride-induced aortic aneurysms in rabbits[9]. In the present experiments the influx of macrophages into calcium chloride-injured aorta was enhanced, to a similar extent, by the co-application calcium chloride and MCP-1, *C. pneumoniae* or the non-specific macrophage activator thioglycollate. The ability of these preparations to promote macrophage influx into the aortic media was increased, usually by more than twofold, when rabbits were fed a cholesterol-enriched diet. However, although MCP-1 stimulated macrophage influx, this was not associated with aortic dilatation. Both *C. pneumoniae* and thioglycollate appeared to have additional effects to provoke localized aortic dilatation or aneurysm formation,

Table 2 Aortic diameters and macrophage infiltration in cholesterol-fed rabbits

	n	Mean aortic diameter (mm) Start	 3 weeks	Mean macrophage count per unit area at 3 weeks
Control	4	2·8(0·4)	3·0(0·5)	6(6)
Thioglycollate 1 mol/l	4	2·8(0·4)	4·8(0·4)§	288(102)‡
MCP-1				
Human 1 μg	4	3·5(0·4)	4·3(0·3)	340(215)‡
Rabbit 1 μg	4	3·5(0·6)	3·5(0·7)	157(250)‡
Cytokine cocktail*	2	3·0(0·0)	3·0(0·0)	31(20)
Chlamydia pneumoniae†				
Heat inactivated	4	2·4(0·2)	3·5(0·5)	27(15)
Formalin fixed	5	2·4(0·7)	4·3(0·6)§	143(69)‡
Live	4	2·0(0·5)	4·3(1·3)§	324(144)‡

Values are mean(s.d.). All agents were added to calcium chloride 0·2 mol/l. *Monocyte chemoattractant protein (MCP) 1, tumour necrosis factor α and interleukin 1β, 1 μg each. †0·5 × 10^8 organisms. ‡$P < 0·01$ *versus* no additive (analysis of variance); §$P < 0·02$ *versus* initial diameter (paired *t* test) perhaps through mechanisms of macrophage protease activation and secretion.

Previously in a rabbit iliac artery injury model, hypercholesterolaemia was an important stimulus for both monocyte chemotaxis and monocyte activation[12]. In the present study, hypercholesterolaemia did not appear to be a sufficient stimulus for the macrophage influx. Even after stimulation of macrophage influx with the MCP-1, the macrophages did not appear to cause aortic dilatation. Although high doses of recombinant MCP-1 were used, neither the human nor rabbit recombinant MCP-1 was glycosylated. It is possible that only the native glycosylated forms of this chemokine exhibit full biological activity[13,14]. Therefore, any conclusions concerning the role of MCP-1 must be made with caution. Curiously, the influx of macrophages was no greater in response to rabbit MCP-1 than with human MCP-1; addition of TNF-α and IL-1β in a cytokine cocktail suppressed the ability of MCP-1 to recruit macrophages.

It was of particular interest that *C. pneumoniae*, albeit at high doses, provoked both macrophage influx and aneurysm formation. Similar concentrations of this organism given intranasally have been used to cause other arterial pathology, particularly intimal thickening, in rabbits[15,16]. Live organisms do not seem to be essential for aneurysm formation, since the formalin-fixed preparations were almost as efficacious. Both live and formalin-fixed preparations have preservation of protein antigens[17]. In contrast, protein antigens are largely destroyed in heat-inactivated preparations, although the lipopolysaccharide remains intact[17]. The effect of heat-inactivated preparations on both macrophage influx and aortic dilatation was considerably less than that of the live or formalin-fixed preparations and the DNA evidence suggested that the heat-inactivated organisms did not remain in the aorta, but were cleared by the reticuloendothelial system. Therefore, these preliminary results suggest that chlamydial antigens stimulate macrophage influx and aortic dilatation; these antigens are likely to be either membrane proteins or heat-shock proteins[17–20]. Chlamydial heat-shock proteins have been shown previously to activate macrophages and other vascular cells, with increased secretion of metalloproteinases[17,18]. Metalloproteinases appear to have an important role in aneurysm development[1]. Unfortunately, in the present study there was insufficient unfixed material to investigate the effect of chlamydial preparations on metalloproteinase activity.

The two important findings of this study are that macrophage influx alone is insufficient to provoke acute experimental aortic dilatation and that chlamydial antigens can provoke acute experimental aortic dilatation. Although extreme hypercholesterolaemia was necessary in the experimental model, these findings may have relevance to the pathogenesis of human aortic aneurysms, which can occur following acute aortitis with syphilis or other bacteria. There is no suggestion that *C. pneumoniae* causes acute aortitis in humans. However, in human aorta, *C. pneumoniae* infection may add to the aggregate pathogen burden by stimulating macrophage activation and proteolysis in the vessel wall. There is a precedent for this[17,18]. *C. pneumoniae* replicates within macrophages, but if its antigens or heat-shock proteins are sufficient to stimulate aortic dilatation, antibiotic treatment may be insufficient to reduce the potential effects of this organism on proteolysis in the aneurysm wall.

Acknowledgements

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A single normal ultrasonographic scan at age 65 years rules out significant aneurysm disease for life in men

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Background: Screening for abdominal aortic aneurysm (AAA) has been carried out in Gloucestershire since 1990. All men in the county are offered aortic ultrasonography in their 65th year. Men with an aortic diameter of less than 26 mm are considered 'normal' and no follow-up is arranged. The aim of this study was to ascertain if men with 'normal' aortic diameters at age 65 years ever develop a clinically significant aneurysm.
Methods: A cohort study was performed on 223 65-year-old men who had an aorta of less than 26 mm in diameter in 1988. These men had repeat ultrasonography in 1993 and 2000. The causes of death in men who died during this interval were investigated.
Results: Eight men were lost to follow-up. As far as it was possible to ascertain, none of the 86 men who died over the 12-year interval did so from ruptured AAA. There was no clinically significant increase in mean aortic diameter in the remaining 129 men who had three serial ultrasonographic scans over the 12-year interval.
Conclusion: A single, 'normal' ultrasound scan at age 65 years effectively rules out the risk of clinically significant aneurysm disease for life in men.

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Introduction

Ruptured abdominal aortic aneurysm (AAA) is a major and increasing cause of death in men over 65 years of age, accounting for an estimated 6000 deaths annually in England and Wales[1]. Screening for AAA has been taking place in Gloucestershire since 1990. Men are offered aortic ultrasonography in their 65th year, performed at an annual visit to each general practitioner (GP) surgery in the county. Subjects with an anteroposterior aortic diameter of 26 mm or greater on ultrasonographic imaging are considered at risk of further aortic growth and are therefore reimaged annually in the surgery. Men with an aortic diameter of over 40 mm are referred to the surgical clinic where they are reviewed biannually and offered aneurysm repair if the aortic diameter exceeds 55 mm. The screening project has reduced the mortality rate from ruptured AAA within the screened portion of the population[2].

The question remains of whether any further follow-up is necessary in men with a 'normal' aorta at age 65 years. Work done in Gloucestershire by Emerton *et al.*[3] in 1993 showed that men with an aortic diameter of less than 26 mm at 65 years did not develop clinically significant AAA by the age of 70 years. The aim of the present study was to review this same cohort of men at age 77 years to determine if any had developed a clinically significant aneurysm.

Patients and methods

In 1988, in a pilot study for the Gloucestershire Aneurysm Screening Programme, 906 men between the ages of 65 and 74 years were examined by aortic ultrasonography[4]. These subjects were the patients of four GP practices participating in the pilot study and represent the 76 per cent who attended for ultrasonographic examination following invitation of all male patients in this age range registered with the practices. Within this group there were 236 men aged 65 years. Thirteen (6 per cent) of these 65-year-old men had an aortic diameter of 26 mm or greater and therefore remained under annual follow-up. The remaining 223 (94 per cent) had a 'normal' scan with an aortic diameter of less than 26 mm and were therefore not followed routinely. These 223 men were invited for a second scan in 1993, by which time 28 had died and three were lost to follow-up. Thus 192 men underwent a second aortic ultrasonographic scan at age 70 years[3].

These 192 men were invited for a third scan in 2000 and form the basis of this study. In the interval between 1993 and 2000 a further 58 men had died and five more were lost to follow-up, leaving 129 men who had a third scan (*Fig. 1*).

To organize this follow-up, each subject was contacted via the GP and invited to attend the GP surgery for an ultrasonographic scan. Those not fit enough to attend the GP practice were offered a home visit. All of these men had ultrasonography of the aorta by one of a team of four aneurysm screening radiographers, using methodology described previously[5]. The few men who had moved outside Gloucestershire were contacted via their new GP and offered a scan within their locality.

Results

Men who died or were lost to follow-up

Of the eight men lost to follow-up, four remain within the county of Gloucestershire and were either unwilling or unfit to undergo further ultrasonography, while four have moved from the area and, to date, have not been re-examined. In all cases, contact was made with either the subject or his GP, confirming that the patient remained alive and that no diagnosis of aortic aneurysm had been made.

None of the 86 men who died during follow-up had ruptured AAA recorded as the cause of death on the death certificate. The majority of the men died from causes not easily confused with ruptured AAA, such as pulmonary disease, stroke or malignancy (*Fig. 2*). The 14 deaths classified as miscellaneous have all been examined in detail and confirmed. None is likely to have been confused with a ruptured aortic aneurysm and the group includes causes such as fractured neck of femur, perforated duodenal ulcer and death in an air crash. If a ruptured AAA had been missed, it would seem most likely that it would have been wrongly certified as a myocardial infarction (MI). Of the 27 men with MI recorded as the cause of death, six had this diagnosis confirmed at autopsy and seven were certified in hospital with clinical, electrocardiographic and biochemical confirmation of the diagnosis. This left 14 men who died and were certified in the community by the GP. For the group who died from MI as a whole, the mean interval since the final aortic ultrasonographic scan was 2·5 years; 26 of the 27 men last had a measured aortic diameter below the 26-mm threshold. The remaining subject had an aortic diameter of 31 mm, but was imaged only 6 months before his death. It would therefore seem extremely unlikely that any of these 86 deaths was due to ruptured AAA, although this is impossible to prove absolutely without performing post-mortem studies on all the men who died.

Men who had all three ultrasonographic scans

Among the remaining 129 men, who had all three scans, there was no clinically significant increase in the mean aortic diameter over the 12 years (*Fig. 3*). The mean diameters in 1988, 1993 and 2000 were 18·9, 19·0 and 20·2 mm respectively. There was, however, a progressive upward skewing of the range of aortic diameters. For the scans performed in 2000, this upward drift was explained by four men with aortic diameters of 32, 34, 34 and 36 mm respectively. At the time of the final scan, these men were all aged 77 or 78 years. Aneurysm repair is seldom indicated unless the aortic diameter is at least 55 mm. It would

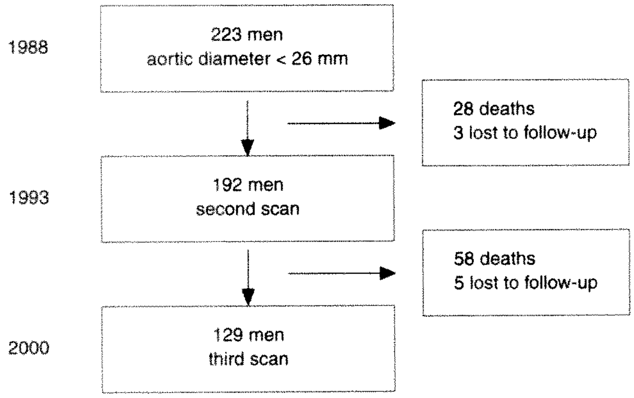

Fig. 1 Progress of the cohort of men, aged 65 years in 1988, over the 12-year interval

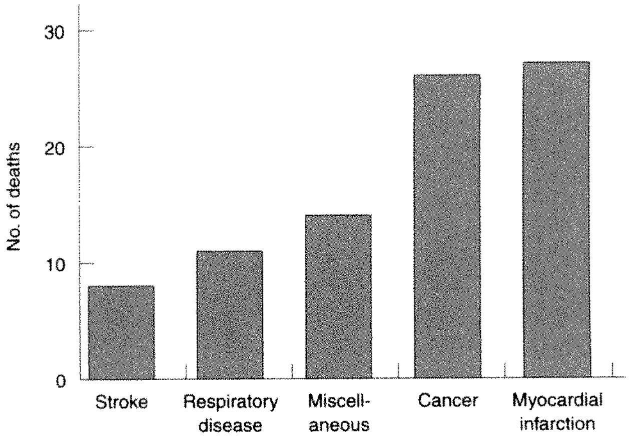

Fig. 2 Causes of death of 86 patients

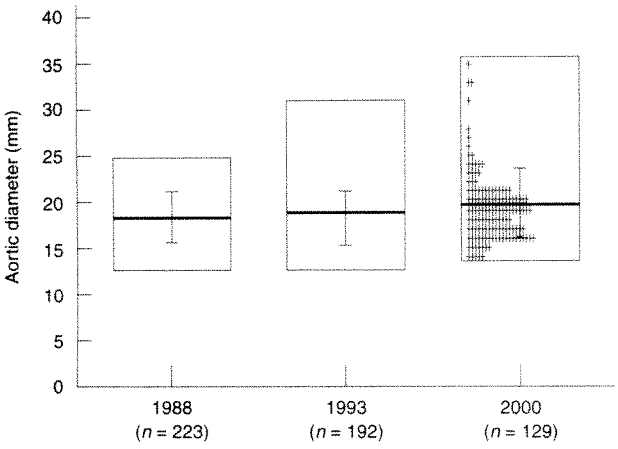

Fig. 3 Aortic diameters measured on serial ultrasonographic scans in men with an aortic diameter of less than 26 mm at age 65 years in 1988. Mean, s.d. and ranges are shown as horizontal bars, error bars and boxes respectively. Individual aortic diameters are marked for scans performed in 2000

therefore seem extremely unlikely that even the men with the largest aortas would ever develop a clinically significant AAA that would warrant treatment by elective surgery.

Discussion

In deciding whether a screening programme is feasible, certain criteria must be met. AAA lends itself to screening, as it is a serious and relatively common condition which often remains asymptomatic until rupture, with its associated high mortality rate. AAA has a well understood aetiology and disease progression. Aortic ultrasonography is an excellent screening tool as it is cheap, non-invasive, reliable and widely acceptable to the screened population. The role of elective aneurysm repair is well established in the management of AAA[6], providing an effective treatment for the condition if uncovered at screening. In Gloucestershire, screening has not dramatically increased the number of aneurysm repairs performed in the county[2]. Recently it has been shown that the mortality rate from ruptured AAA was reduced within the screened portion of the population[2] and that the postoperative mortality rate following the repair of a screen-detected aneurysm was lower than that for those detected incidentally[7]. Early detection of the disease by screening therefore seems to be advantageous. Work done in Chichester has paved the way for a large multicentre randomized trial comparing the mortality rate from AAA in screened and unscreened groups of men[8]. If the results of this trial concur with the previous data in showing a survival advantage within the screened population, a strong argument could be made for instigatation of a national screening programme for AAA.

Opponents of such a programme argue that significant psychological distress is caused to men with an enlarged aorta at ultrasonography, and that many of these men will never develop an AAA of sufficient size to warrant elective repair. While one study supports this point of view[9], a report from this country has shown minimal psychological impact[10]. Uncertainty also exists in determining who to screen, at what age and which threshold of aortic diameter to use. In Gloucestershire only men are screened as AAA is ten times more prevalent in men than women. This study has shown that a man with an aortic diameter of less than 26 mm at age 65 years will not subsequently develop a clinically significant AAA. This is a major advantage for the strategy of imaging at 65 years as it allows the majority of men to be reassured and released from follow-up after a single ultrasonographic scan. This advantage, however, has to be balanced against the fact that 9 per cent of ruptured AAAs in men occur under the age of 65 years and would therefore be missed by this method of screening. If all men were screened at age 60 years, more ruptured aneurysms could be avoided. However, it is not known whether an ultrasonographic scan showing an aortic diameter of less than 26 mm at age 60 years would still rule out the development of AAA. A second scan might be needed later, which would double the costs of screening.

The choice of 26 mm as the cut-off for a 'normal' aortic diameter is, similarly, a compromise and was chosen somewhat arbitrarily at the beginning of the study to include 95 per cent of the male population aged 65 years. If 30 mm was used at age 65 years, only 2 per cent, as opposed to 5 per cent, of the screened population would require follow-up (unpublished data), reducing not only the cost of the screening programme, but any psychological impact. The use of a 30-mm threshold, however, would mean that a small number of men would develop an AAA in their late 70s (unpublished data).

The experience gained in Gloucestershire has shown that the 26-mm threshold, used at age 65 years, not only provides reassurance about the likelihood of future AAA but also provides a manageable number of patients requiring follow-up[2]. A 26-mm threshold also allows for the 3-mm margin of error[11] associated with the ultrasonographic technique.

In conclusion, if a national aortic aneurysm screening programme is to be commenced, use of the Gloucestershire screening model would allow the great majority of men screened at the age of 65 years to be reassured that they are extremely unlikely ever to develop a significant aortic aneurysm. It also provides a manageable number of men requiring further follow-up and intervention.

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Association between plaque instability, angiogenesis and symptomatic carotid occlusive disease

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Background: Angiogenesis is a recognized feature of the atherosclerotic process and has been described in the context of unstable coronary atherosclerotic lesions. The aim of this study was to assess the association between angiogenesis in atherosclerotic carotid plaques and microscopic features of plaque instability, in particular intraplaque haemorrhage.

Methods: Consecutive patients undergoing carotid endarterectomy were included. Endarterectomy specimens were divided into their constituent atherosclerotic lesions. Histological sections were prepared and stained with haematoxylin and eosin, and immunohistochemically with an endothelial cell marker (CD34). The quantity of intraplaque haemorrhage was measured in transverse histological sections using computerized image analysis. Microvessel counts were performed in CD34-stained sections and were verified through computerized image analysis.

Results: Some 239 atherosclerotic lesions from 73 patients were available for analysis; 73 were early lesions, 74 were raised fibroatheromas and 92 were unstable atherosclerotic plaques. One hundred and fifty lesions were not haemorrhagic; 89 exhibited intraplaque haemorrhage, of which 28 involved less than 50 per cent of the plaque sectional area. There were higher microvessel counts in plaques containing over 50 per cent haemorrhage ($P < 0.0001$), unstable atherosclerotic lesions ($P < 0.0001$) and atherosclerotic lesions obtained from symptomatic patients ($P < 0.001$).

Conclusion: There are strong associations between plaque vascularity, quantity of intraplaque haemorrhage and presence of symptomatic carotid occlusive disease.

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Introduction

Atherosclerosis in the carotid bifurcation is a complex and dynamic process. Plaque rupture and haemorrhage occur frequently during the natural history of atherosclerotic lesions and have been implicated in the development of the associated clinical syndromes[1,2].

Intimal angiogenesis is a well recognized feature of atherosclerotic lesions. Angiogenesis is implicated in the development of atherosclerosis and associated clinical syndromes in the coronary circulation[3,4], and in the context of symptomatic carotid occlusive disease[5,6]. It has been suggested that these new blood vessels are inherently weak and therefore responsible for development of intraplaque haemorrhage, sudden increase in plaque volume and the development of plaque instability[7].

The aims of this study were to examine the relationship between morphological characteristics of atherosclerotic lesions, the quantity of intraplaque haemorrhage and the extent of angiogenesis in carotid atherosclerotic lesions, and to relate the significance of these findings to the development of symptomatic carotid occlusive disease.

Patients and methods

Consecutive patients undergoing carotid endarterectomy at St Vincent's University Hospital between July 1999 and May 2000 were included in the study. Permission of the ethics committee at St Vincent's University hospital was obtained before starting the study. Informed consent was obtained from all subjects.

Immediately after operation, carotid endarterectomy specimens were placed in normal saline. They were examined and photographed. They were then fixed in 10 per cent formaldehyde solution for 24 h and decalcified in 5 per cent ethylenediamine tetra-acetic acid solution for 48 h.

Table 1 American Heart Association classification of atherosclerotic lesions[10]

AHA class	No. of lesions	Definition
II	4	Raised thickened intima
III	27	Pre-atheroma, intimal macrophages, deeper pools of extracellular lipids
IV	42	Stable flat atheroma (definite core)
V	74	Stable raised fibroatheroma
VI	92	Unstable atherosclerotic lesions (haemorrhage, ulceration, necrotic core)

American Heart Association (AHA) classes: II, III, IV, early lesions; V, stable, raised fibroatheromas; VI, unstable atherosclerotic lesions

Each specimen was opened through the surgical arteriotomy in the anterolateral aspect of the specimen, examined and divided into constituent atherosclerotic lesions. Each atherosclerotic lesion was identified grossly as a raised area within the specimen with a clear shoulder proximally and distally. Early lesions were obtained from areas of thickened intima in the proximal and distal extents of the endarterectomy. A similar technique has been described by Jeziorska *et al.*[8,9].

Transverse paraffin blocks 4 mm thick were prepared from each atherosclerotic lesion. Sequential transverse sections 4 μm apart were obtained from each block and stained with haematoxylin and eosin, and immunohistochemically with monoclonal antibodies to an endothelial cell marker (CD34, Q-Bend clone; Dako™ Corporation, Carpinteria, California, USA). Secondary antibody staining was performed using an avidin–biotin complex staining kit (Vector Laboratories, Burlingame, California, USA). Diaminobenzidine was used as the chromogen.

Plaque morphology was assessed using the American Heart Association classification for atherosclerotic plaques[10] (*Table 1*).

Microvessel counts were performed for the whole plaque and the plaque cap, by a single observer, and verified by means of an image analysis system. Each microvessel was defined as a lumen surrounded by a rim of endothelial cells highlighted by immunostaining with anti-CD34 antibodies. The total microvessel count for each atherosclerotic plaque section was divided by the area covered by that section. This was measured by computerized image analysis. Microvessel counts were expressed as microvessels per square centimetre of plaque sectional area.

Image analysis

Digital image analysis was used to validate manual microvessel counts and measured the area covered by fresh intraplaque haemorrhage in sections obtained from each atherosclerotic lesion. Images were captured through a microscope-mounted high-resolution digital camera with a video output (Olympus CAMEDIA C-2000 z) mounted through a purpose-built microscopic C-mount on an Olympus BX-40 microscope (Olympus, Tokyo, Japan).

Five randomly selected high-powered fields were obtained from the plaque cap, and ten from the rest of the plaque section at × 400 magnification. The images were saved as bitmap images and transferred on to the image analysis computer workstation using a Smart Media card (MAFP-2 Flash Path®; Olympus).

The image analysis workstation used was a purpose-built Pentium® III microprocessor (Intel Corporation, Athlone, Ireland) with 450-MHZ processing speed and 256 megabytes of Random Access Memory. Images were analysed with the Adobe PhotoShop professional Version 4 image analysis software (Adobe, Mountain View, California, USA). This involved measurement of the total stained area by performing counts of image pixels with colour characteristics similar to the immunostained area. This was then expressed as a percentage of total image size by reviewing histograms on the image analysis workstation.

Cross-sectional images from the haematoxylin and eosin-stained transverse sections of the atherosclerotic lesion were obtained at × 100 magnification. These images were saved as a bitmap and used to quantify the area covered by plaque haemorrhage in each section. Each section was photographed and a composite image of the atherosclerotic plaque section was constructed (*Fig. 1*).

Representative areas from sites of fresh intraplaque haemorrhage were selected at × 200 magnification by the identification of red blood cells. These areas were marked by means of a cursor, and colour characteristics of haemorrhagic areas were identified. These colour characteristics were then loaded on to a section mask, which was used to identify plaque haemorrhage in images obtained from transverse section of atherosclerotic lesions. The area covered by haemorrhage was measured and expressed as a function of the total sectional area. The median haemorrhagic area for each section was calculated from all the sections obtained from the same lesion.

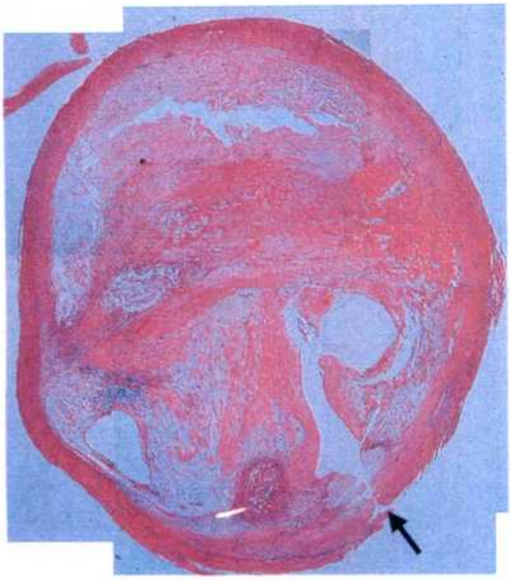

Fig. 1 Section of an unstable atherosclerotic plaque obtained at × 100 magnification at the site of stenosis. The arteriotomy (arrow) serves to orient the image as it is positioned anterolaterally

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 10 computer software (SPSS, Chicago Illinois, USA). Manual microvessel counts were validated by comparing them to corresponding values obtained by digital image analysis. The latter were expressed as median percentage immunostained areas of images of high-powered fields. Linear regression analysis and Bland–Altman analysis[11] were used to compare the two methods of analysing microvessel counts in atherosclerotic lesions.

Kruskal–Wallis and Mann–Whitney tests were used to assess the statistical significance of the differences in microvessel counts between atherosclerotic plaque types. The median microvessel count for all of the atherosclerotic lesions obtained from each patient was calculated. The difference in microvessel counts between symptomatic and asymptomatic patients was analysed with the Mann–Whitney U test. Linear regression analysis was used to study the association between microvessel counts in atherosclerotic lesions and the quantity of intraplaque haemorrhage.

Results

Seventy-three patients (42 men, 31 women) were included in the study; 54 were symptomatic and 19 were asymptomatic before carotid endarterectomy. The median age of the patients was 71 (range 50–87) years.

Examination of the carotid endarterectomy specimens identified 263 discrete atherosclerotic lesions (median 3 (range 2–7) lesions per section), of which 24 could not be analysed owing to extreme calcification ($n = 7$) or intraoperative damage ($n = 17$).

Two hundred and thirty-nine atherosclerotic lesions were available for analysis; 73 were early lesions (American Heart Association (AHA) classes II, III and IV), 74 were raised fibroatheromas (AHA class V) and 92 were unstable atherosclerotic plaques (AHA class VI) (*Table 1*).

Intraplaque haemorrhage

One hundred and fifty lesions did not contain any intraplaque haemorrhage. Intraplaque haemorrhage was present in 89 carotid lesions. The median sectional area covered by intraplaque haemorrhage was 53·2 (range 5·8–87) per cent. In 28 lesions the haemorrhagic area was less than 50 per cent of plaque volume, whereas in 61 lesions the haemorrhagic area was greater than 50 per cent of plaque volume. A significantly higher volume of intraplaque haemorrhage was observed in patients with symptomatic carotid lesions than in asymptomatic patients (median (range) 49·6 (0–86·2) *versus* 4·6 (0–52·1) per cent; $P < 0{\cdot}001$).

Plaque (intimal) vascularity

Angiogenesis was a common feature of all atherosclerotic lesions studied (*Fig. 2*). Intimal capillaries were most numerous in the shoulder region; however, they were also present in the plaque cap and were seen growing into the core from the shoulder area. A common finding in the atherosclerotic plaques studied was macrophage adhesion to the endothelial lining of intraplaque blood vessels (*Fig. 2*). This was more prevalent in unstable atherosclerotic plaques, suggesting that the endothelial cells were activated in these new blood vessels. Macrophage infiltration was present in all atherosclerotic plaque types, but was more numerous in unstable atherosclerotic lesions where it was mainly present in the shoulder region (*Fig. 3*).

The median total microvessel count in the atherosclerotic lesions studied was 117 (range 7–467) microvessels per cm^2. The median area of the lesion covered by microvessels measured by digital image analysis was 2·4 (range 0·1–9·4) per cent. A close correlation was observed between microvessel counts and digital image analysis measurements of plaque vascularity ($r^2 = 0{\cdot}98$, $P < 0{\cdot}0001$). Bland–Altman analysis revealed close agreement between the two

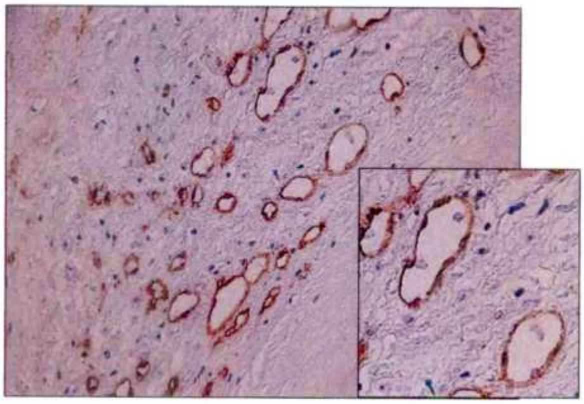

Fig. 2 New blood vessels in the shoulder of an atherosclerotic plaque (original magnification × 400). The enlarged image reveals leucocyte adhesion to the endothelial cells, indicating that these endothelial cells are likely to be activated

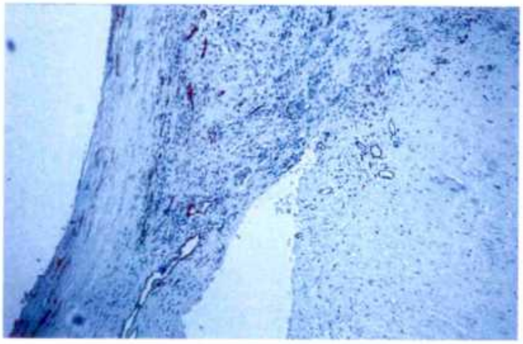

Fig. 3 Atherosclerotic plaque shoulder viewed at × 100 magnification. Note the new blood vessels, which are stained brown indicating that they express CD34 endothelial cell marker

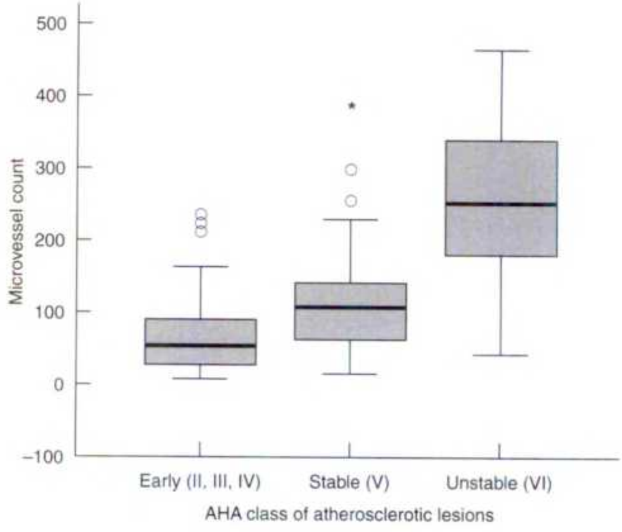

Fig. 4 Microvessel counts (per cm^2) in early atherosclerotic lesions ($n = 73$), stable raised fibroatheromas ($n = 72$) and unstable atherosclerotic lesions ($n = 92$). Values are median. AHA, American Heart Association. $P < 0.001$ (unstable *versus* early and stable lesions, Kruskall Wallis test)

methods of assessment of microvessel density in the atherosclerotic lesions studied.

Higher median (range) microvessel counts were observed in atherosclerotic lesions obtained from the 54 patients with symptomatic carotid occlusive disease (205 (83–412) microvessels per cm^2), compared with those obtained from the 19 asymptomatic patients (78 (36–150) microvessels per cm^2).

There were higher median (range) microvessel counts in plaques containing over 50 per cent haemorrhage (277 (43–467) microvessels per cm^2), compared with those containing less than 50 per cent (172 (57–372) microvessels per cm^2) and non-haemorrhagic plaques (83 (7–389) microvessels per cm^2) ($P < 0.0001$). A close correlation was observed between total microvessel count and the area covered by intraplaque haemorrhage in the corresponding atherosclerotic lesions ($r^2 = 0.44$, $P < 0.001$).

Higher median (range) microvessel counts were observed in unstable atherosclerotic lesions (253 (43–467) microvessels per cm^2) compared with stable fibroatheromas (107 (14–389) microvessels per cm^2) and early atherosclerotic lesions (55 (7–237) microvessels per cm^2) ($P < 0.0001$). No statistically significant difference was observed in the microvessel counts between the stable raised fibroatheromas and early atherosclerotic lesions (*Fig. 4*). Similar findings were observed in the plaque caps of the atherosclerotic lesions studied. Median (range) microvessel counts in the plaque caps of unstable atherosclerotic lesions (AHA class VI) (37 (4–66) microvessels per cm^2) were significantly higher than counts in the plaque caps of stable raised fibroatheromas (12 (0–45) microvessels per cm^2) and early atherosclerotic lesions (8 (0–56) microvessels per cm^2) ($P < 0.001$).

Discussion

Although the presence of new blood vessels in atherosclerotic plaques has been recognized for over 60 years[12], their significance in the development of plaque instability has received attention only recently. In a large post-mortem study Geiringer[13] established that the normal human intima is devoid of blood vessels. He also demonstrated that the intima becomes vascularized only when it proliferates beyond a critical thickness[13].

Immunohistochemical studies of coronary atherectomy specimens have provided evidence of an association between the presence of microvessels in coronary atherosclerotic lesions and the development of unstable angina and myocardial infarction[14]. Tenaglia *et al.*[3] in an immunohistochemical study of coronary atherectomy specimens found that a larger number from patients with unstable angina exhibited angiogenesis.

Recent data from Jeziorska and Woolley[8,9] confirmed the observation that angiogenesis is a prominent feature of the late stages of the carotid atherosclerotic process, often appearing as a plexus of both small and large vessels, and occupying a significant proportion of shoulder areas[8]. Immunostaining atherosclerotic lesions with antibodies against smooth muscle α-actin has demonstrated the presence of small arterioles within the shoulder of established atherosclerotic lesions[8].

Angiogenesis has also been reported in early atherosclerotic lesions and in stable fibroatheromas obtained from carotid endarterectomy specimens, where it provides a focus for local accumulation of macrophages and apolipoprotein A-I and B[9].

McCarthy *et al.*[5] reported a strong association between microvessel counts within atherosclerotic plaques obtained from carotid endarterectomy specimens and the incidence of ipsilateral neurological symptoms within 1 month of the surgical procedure[5]. This finding supports the present study and suggests that plaque angiogenesis may be significant in the development of symptomatic carotid occlusive disease. McCarthy *et al.*[5] also demonstrated significantly higher microvessel counts within the plaque and the fibrous cap of patients who had preoperative or intraoperative evidence of cerebral embolization. Cerebral embolization is a marker of atherosclerotic plaque instability.

Intramural haemorrhage within the carotid artery atherosclerotic plaque has been studied extensively, both because of its association with symptomatic carotid artery disease and because of the insight it may provide into the evolution of carotid artery atherosclerosis. The importance of intraplaque haemorrhage was first described by Imparato *et al.*[14]. Their work revealed that 80 per cent of patients with symptomatic carotid artery stenosis had complicated atherosclerotic plaques at carotid endarterectomy, predominantly due to intraplaque haemorrhage. In later follow-up studies they showed that intramural haemorrhage was the only significant factor common to symptomatic patients and those with a high degree of stenosis or focal symptoms[15]. Other investigators have confirmed the above association[16–18]. The present study revealed a significantly greater quantity of intraplaque haemorrhage in patients with symptomatic carotid occlusive disease.

This study also demonstrated a strong relationship between the quantity of intraplaque haemorrhage and neovascularity within atherosclerotic lesions. The close quantitative relationship between the microvessel content of atherosclerotic lesions and intraplaque haemorrhage highlights the intimacy of their relationship. Fryer *et al.*[7] in a pathological study of carotid endarterectomy specimens demonstrated the presence of new blood vessels within the plaque. These vessels were described as thin walled with an irregular outline. They revealed a significant association between the presence of intimal blood vessels and clinically significant intraplaque haemorrhage[7]. Similar observations have been reported by Milei *et al.*[6], who, in an analysis of 165 carotid endarterectomy specimens, reported a close relationship between intraplaque haemorrhage and neovascularization of the atherosclerotic lesions.

It has been postulated that intraplaque haemorrhage arises as a consequence of subintimal and intramural angiogenesis, resembling vessels seen in tumours[19]. This hypothesis explains the observation that blood vessels in atherosclerotic plaques obtained from patients with symptomatic carotid occlusive disease are irregular in shape and larger in cross-sectional area than those obtained from patients who were asymptomatic before endarterectomy[5,7]. Lusby *et al.*[1] considered that angiogenesis within carotid atherosclerosis might render these lesions prone to mechanical stress and therefore result in intraplaque haemorrhage. Bornstein *et al.*[18] in a study of 77 consecutive atherosclerotic lesions observed that intraplaque haemorrhage is usually deep and infrequently connected with the vessel lumen. The presence of old haemorrhage deep within the body of the atherosclerotic lesion suggests that the bleeding originates locally[6].

Another feature of these new blood vessels is their association with mononuclear and macrophage infiltration in the atherosclerotic plaques[20]. Increased expression of E-selectin, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 has been noted in areas of plaque vascularization. Expression of these cell adhesion molecules suggests that endothelial cells lining these vessels are activated[21]. Activation results in leucocyte adhesion and migration into the atherosclerotic lesion. Inflammatory activity in the plaque cap region of atherosclerotic lesions obtained from carotid endarterectomy specimens has been associated with a higher incidence of preoperative ischaemic neurological events[22]. The microvessels present in the plaque caps of unstable atherosclerotic lesions might be a local source of activated endothelial cells, responsible for leucocyte adhesion and migration. Infiltration of leucocytes and other inflammatory cells is associated with destabilization of the atherosclerotic lesion through the release of proteases, most notably of the matrix metalloproteinase family[23], and secretory smooth muscle cell loss could be responsible for formation of the fibrous plaque cap[24].

The significance of plaque neovascularity may go beyond its importance as a causative element of intraplaque haemorrhage. These new blood vessels, by providing the necessary conduits for the transfer of nutrients, growth factors and metabolic products, could play an active role in the metabolic activity of the plaque and ultimately control the processes that govern plaque progression.

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Differences in the detection of cyclo-oxygenase 1 and 2 proteins in symptomatic and asymptomatic carotid plaques

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Background: The expression of cyclo-oxygenase (COX) 1 and 2 has been demonstrated in atherosclerotic arteries. In the present study this was correlated with symptoms arising from a carotid plaque.

Methods: Carotid plaques from 12 asymptomatic patients were compared with 11 plaques from patients who had had neurological symptoms within the preceding 30 days. Sections were stained with haematoxylin and eosin, elastin van Gieson and goat antihuman antibodies to COX-1 and COX-2. Plaque morphology was correlated with neurological symptoms. The area with positive COX-1 and COX-2 staining was measured by computerized planimetry in entire cross-sections and in specific areas of the plaque.

Results: There was a significant association between cap thinning and plaque rupture with symptoms ($P = 0{\cdot}003$). The percentage area of positive staining in entire cross-sections for both COX-1 and COX-2 was significantly greater in symptomatic plaques ($P = 0{\cdot}001$ and $0{\cdot}0004$ respectively). Staining in symptomatic plaques was significantly greater in the cap (COX-1: $P = 0{\cdot}001$; COX-2: $P = 0{\cdot}0001$) and shoulder (COX-1: $P = 0{\cdot}008$; COX-2: $P = 0{\cdot}007$) regions of the plaque. COX-1 expression in the sclerotic area was not increased ($P = 0{\cdot}15$) although COX-2 staining was significantly greater ($P = 0{\cdot}04$).

Conclusion: Both COX-1 and COX-2 detection was increased in symptomatic plaques. COX may contribute to plaque rupture and the onset of symptoms.

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Introduction

Carotid artery atherosclerosis is an important cause of thromboembolic ischaemic stroke[1], which may result in disability or death[2,3]. Although more severe stenoses are associated with an increased risk of neurological events[4–6], comparison of the natural history of symptomatic and asymptomatic patients with similar degrees of carotid stenosis suggests that other factors may be responsible for the development of plaque instability and symptoms[6–10]. Previous reports comparing the histological characteristics of symptomatic and asymptomatic plaques indicate that thinning, rupture and macrophage infiltration of the collagen cap are associated with the onset of symptoms[11]. Furthermore, accumulation of macrophages in the cap appears to be greater in recently symptomatic plaques[12]. Identification of the mechanisms that link macrophage accumulation to disruption of the collagen cap might form the basis of therapeutic strategies that promote plaque stability.

In vitro studies using stimulated macrophages have shown that increased production of prostaglandin (PG) E_2 is responsible for augmented expression of metalloproteinases[13,14] and collagen lysis. Further, PGE_2 inhibits collagen synthesis by vascular smooth muscle cells (VSMCs)[15,16]. Both these processes have important implications for plaque stability[13–16]. In addition, PGE_2 promotes angiogenesis[17], which may increase the risk of intraplaque haemorrhage and plaque rupture[18].

Prostaglandin synthesis from arachidonic acid is controlled by cyclo-oxygenase (COX) which exists in at least two isoforms (COX-1 and COX-2). Each of these is encoded by independently regulated genes[19]. These isoforms also demonstrate differing substrate affinity and inhibitor selectivity[19]. Although previous reports by Baker *et al.*[20], Schonbeck *et al.*[21] and Stemme *et al.*[22] have noted differential expression of COX-2 in atheroma, with COX-1 being present in normal arteries and thus likely to have a constitutive role, their individual contribution to plaque instability and symptoms remains unknown.

Table 1 Demographic and clinical risk factors in patients undergoing carotid endarterectomy

	Symptomatic (*n* = 11)	Asymptomatic (*n* = 12)	*P*
Age (years)*	63 (46–82)	69 (48–77)	0·3†
Men	8	7	0·4‡
Hypertension	8	6	0·2‡
Diabetes mellitus	2	2	0·7‡
Hyperlipidaemia	5	5	0·6‡
Current smoker	7	7	0·6‡
Aspirin therapy (low dose)	11	12	1‡
Other NSAIDS/steroids	None	None	–

*Values are median (range). NSAID, non-steroidal anti-inflammatory drug. †Mann–Whitney *U* test. ‡Fisher's exact test

The present study aimed to determine whether instability of human carotid atherosclerotic plaques, and therefore cerebral ischaemic symptoms, is associated with increased detection of COX-1 and/or COX-2 proteins.

Patients and methods

Carotid endarterectomy specimens were collected from a consecutive cohort of 40 patients, 12 of whom had never experienced neurological symptoms. Of the 28 symptomatic patients 11 had experienced symptoms during the 30 days preceding endarterectomy. This study involved a comparison of plaques from the 11 recently symptomatic patients and those from 12 asymptomatic patients, two groups at the extreme ends of the spectrum of symptomatology. In the symptomatic group, six presented with transient ischaemic attack (TIA) (four with crescendo TIAs) while five had suffered a completed stroke. Asymptomatic patients had surgery for non-hemispheric symptoms with a contralateral internal carotid artery occlusion (n = 3) or were patients with a greater than 90 per cent stenosis due to undergo coronary artery bypass grafting (n = 9). None of the asymptomatic patients admitted to a history of neurological symptoms on direct questioning; none underwent cerebral imaging for silent infarcts. All had a 70–99 per cent carotid stenosis as assessed by colour duplex ultrasonography. The hospital research ethics committee approved this project. Demographic details were similar for the two groups of patients (*Table 1*).

The surgical technique was modified to allow removal of an intact carotid endarterectomy specimen from the common, external and internal carotid arteries. The specimens were placed in 4 per cent paraformaldehyde solution and then decalcified in ethylenediamine tetra-acetic acid for 48 h. Transverse sections were made at 3-mm intervals and embedded in paraffin. Serial sections 5 μm thick from each block were stained with haematoxylin and eosin, elastin van Gieson and with goat polyclonal antihuman COX-1 and COX-2 antibodies.

Sections for immunohistochemistry were deparaffinized in xylene, rehydrated in graded alcohols, and preincubated with 0·5 per cent hydrogen peroxide in methanol. Antigen unmasking was carried out by pressure cooking for 2 min. Sections were then incubated with 10 per cent casein and the primary antibody, an affinity-purified goat polyclonal antibody against either human COX-1 or COX-2 (Santa Cruz Biotechnology, Santa Cruz, California, USA), was applied at a dilution of 1 : 25. Immunolabelling was detected with a biotinylated secondary antibody and an avidin–biotin peroxidase complex (Dako Duet™; Dako, Cambridge, UK), and visualized with diaminobenzidine. Sections of carotid plaque from which the primary antibody was omitted were run concurrently as negative controls. The specificity of the COX-1 and COX-2 antibodies was confirmed by negative staining following incubation of the antibodies with the relevant peptides (*Fig. 1*).

Light microscopy

An experienced histopathologist assessed all haematoxylin and eosin- and elastin van Gieson-stained sections blind for rupture, intraplaque haemorrhage, necrosis and thinning of the cap. Plaque rupture was defined as disruption of the fibrous cap, intraplaque haemorrhage as the presence of blood and/or thrombus within the plaque, and necrosis as the presence of cells with fragmented nuclei in and around the lipid core. Finally, a thin fibrous cap was defined as one in which the lipid and necrotic core and/or foamy macrophages were seen immediately beneath the luminal endothelium. The latter observation was considered significant if it was seen in more than one adjacent cross-section.

Quantification of cyclo-oxygenase staining

Three sections from each plaque, the section showing plaque rupture or minimal cap thickness and the two adjacent sections, were analysed for percentage area of positive immune staining. Images were acquired using a trinocular light microscope (Dialux™ 20EB; Leica, Milton Keynes, UK) via a colour video camera (TK-1280; JVC, Japan) and the area stained was quantified by computerized planimetry using a Qwin® image analysis package (Leica Imaging Systems, Cambridge, UK). To achieve consistency in colour detection, the colour detection threshold of the computer was fixed. The threshold used was chosen by averaging the values obtained independently by two observers. The colour detection and percentage area occupied by the colour is calculated automatically by the

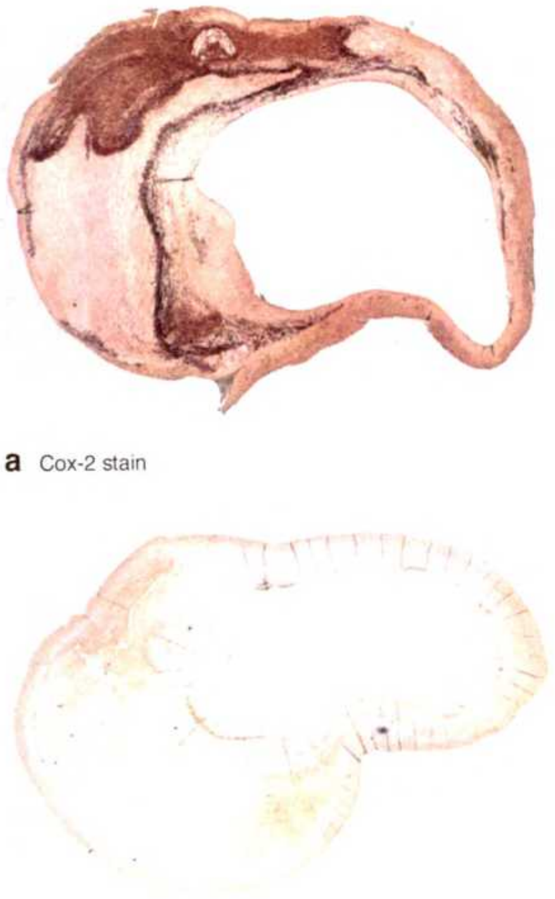

Fig. 1 **a** Cyclo-oxygenase (COX) 2 (diaminobenzidine, brown) dark staining and **b** negative staining of an entire cross-section of a human carotid atherosclerotic plaque. In **b** the antibody applied had been incubated previously with COX-2 protein, confirming the specificity of the stain (original magnification × 7)

computer. Even so, computer planimetry was performed blind with the percentage area of positive staining being determined in the entire cross-section of the plaque, and within the cap, shoulders and remainder of the cross-section (sclerotic component). The cap was defined as the tissue between the lipid core and the vessel lumen, and the shoulder regions as the tissue adjacent to the cap and lipid core (*Fig. 2*). The percentage of COX staining for each component of the plaques was calculated as the mean of the three sections analysed from each plaque. To assess both interobserver and intraobserver variability these measurements were repeated with new outlines being drawn to define the specific areas of the plaque.

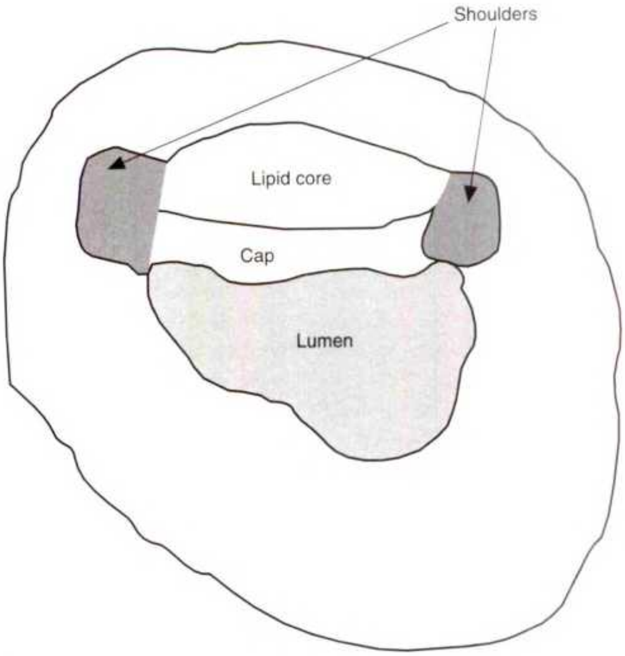

Fig. 2 Definition of the cross-sectional areas of a carotid plaque

Statistical analysis

Non-parametric continuous variables are shown as median (interquartile range) and were compared using the Mann–Whitney *U* test[23]. Categorical data were analysed with Fisher's exact test[23]. $P < 0.05$ was considered significant. The observer variability of computerized planimetry was tested according to the method of Altman and Bland[23].

Results

Cyclo-oxygenase protein in the entire cross-section of carotid plaques

Both COX-1 and COX-2 were detected in macrophages, luminal and neovessel endothelium, and VSMCs. The percentage area of both COX-1 and COX-2 positive staining in symptomatic plaques was significantly greater than that in asymptomatic plaques ($z = 3.2$, $P = 0.001$ and $z = 3.5$, $P = 0.0004$ respectively). These results are summarized in *Fig. 3*.

Cyclo-oxygenase protein in specific areas of carotid plaques

Comparison of the percentage area of staining for COX-1 in symptomatic *versus* asymptomatic plaques indicated that this was greatest in the cap ($z = 3.3$, $P = 0.001$) and shoulder

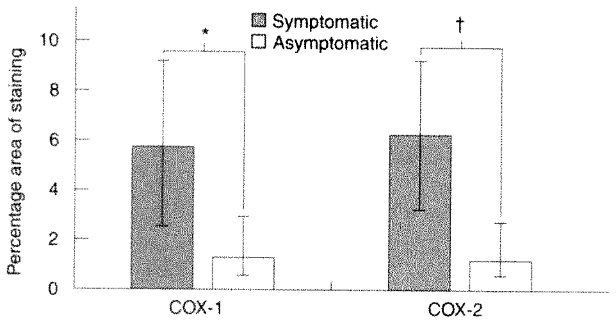

Fig. 3 Median (interquartile range) percentage area expression of cyclo-oxygenase (COX) 1 and 2 in the entire cross-section of the carotid plaque. *$P = 0{\cdot}001$, †$P = 0{\cdot}0004$ (Mann–Whitney *U* test)

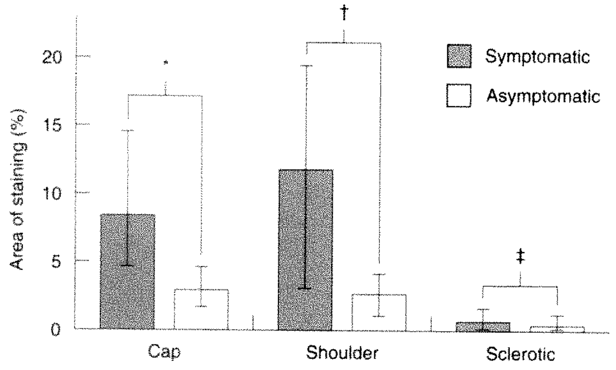

Fig. 4 Median (interquartile range) percentage area expression of cyclo-oxygenase 1 in specific areas of the carotid plaque. *$P = 0{\cdot}001$, †$P = 0{\cdot}008$, ‡$P = 0{\cdot}15$ (Mann–Whitney *U* test)

($z = 2{\cdot}6$, $P = 0{\cdot}008$) regions (*Fig. 4*). No differences were observed for the sclerotic component ($z = 1{\cdot}4$, $P = 0{\cdot}15$).

COX-2 staining was greater in all three components of the symptomatic plaques (cap: $z = 3{\cdot}8$, $P = 0{\cdot}0001$; shoulder: $z = 2{\cdot}7$, $P = 0{\cdot}007$; sclerotic component: $z = 1{\cdot}9$, $P = 0{\cdot}04$) compared with asymptomatic plaques (*Fig. 5*) .

Within-group comparison of COX-1 and COX-2 staining of the cap and shoulder regions compared with the sclerotic component revealed that staining for both COX-1 and COX-2 isoforms was markedly increased in the cap and shoulder regions in plaques from symptomatic patients (COX-1: cap *versus* sclerotic $z = 3{\cdot}6$, $P = 0{\cdot}0003$; shoulder *versus* sclerotic $z = 2{\cdot}9$, $P = 0{\cdot}0003$. COX-2: cap *versus* sclerotic $z = 3{\cdot}6$, $P = 0{\cdot}003$; shoulder *versus* sclerotic $z = 2{\cdot}8$, $P = 0{\cdot}006$) (*Fig. 6*).

Although both COX-1 and COX-2 staining was significantly lower in asymptomatic plaques there remained regional differences between the three components of the plaque (COX-1: cap *versus* sclerotic $z = 3{\cdot}8$, $P = 0{\cdot}0001$; shoulder *versus* sclerotic $z = 3{\cdot}5$, $P = 0{\cdot}0005$. COX-2: cap *versus* sclerotic $z = 2{\cdot}4$, $P = 0{\cdot}01$; shoulder *versus* sclerotic $z = 2{\cdot}1$, $P = 0{\cdot}03$) (*Fig. 7*).

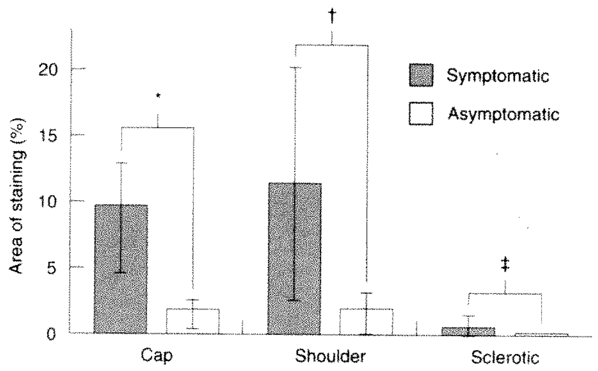

Fig. 5 Median (interquartile range) percentage area expression of cyclo-oxygenase 2 in specific areas of the carotid plaque. *$P = 0{\cdot}0001$, †$P = 0{\cdot}007$, ‡$P = 0{\cdot}04$ (Mann–Whitney *U* test)

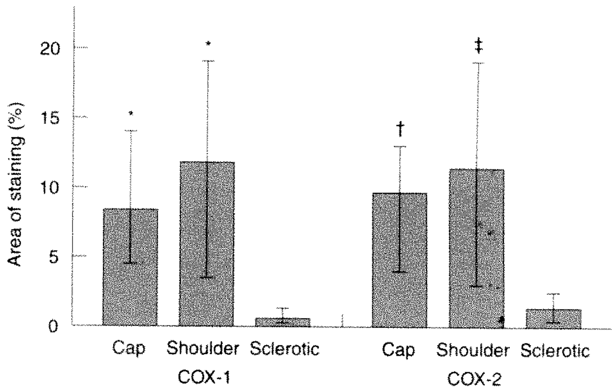

Fig. 6 Median (interquartile range) percentage area expression of cyclo-oxygenase (COX) 1 and 2 in different regions of symptomatic carotid plaques. *$P = 0{\cdot}0003$, †$P = 0{\cdot}0003$, ‡$P = 0{\cdot}006$ *versus* sclerotic (Mann–Whitney *U* test)

Interobserver and intraobserver variability

The mean bias between two independent determinations of percentage area of positive staining in the entire cross-section, cap, shoulder and sclerotic region was 0·5 (95 per cent confidence interval − 1·2 to + 1·0), 0·9 (− 0·4 to + 1·2), 1·3 (− 0·4 to + 1·8) and 0·5 (− 0·8 to + 1·1) per cent respectively. Likewise, the mean bias for repeat measurements by the same observer was 0·3 (95 per cent confidence interval − 0·8 to + 0·7), 0·5 (− 0·5 to + 0·8), 1·0 (− 0·4 to + 1·8) and 0·5 (− 0·8 to + 0·8) per cent respectively.

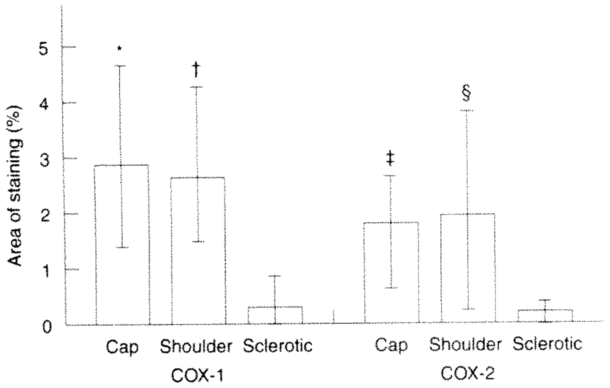

Fig. 7 Median (interquartile range) percentage area expression of cyclo-oxygenase (COX) 1 and 2 in different regions of asymptomatic carotid plaques. *P = 0·0001, †P = 0·0005, ‡P = 0·01, §P = 0·03 *versus* sclerotic (Mann–Whitney U test)

Plaque morphology and symptomatic status

Plaque rupture and cap thinning were significantly more common in symptomatic plaques although intraplaque haemorrhage and plaque necrosis were encountered with similar frequency in asymptomatic plaques (*Table 2*).

Table 2 Plaque morphology and symptomatic status of carotid plaques

	Symptomatic (n = 11)	Asymptomatic (n = 12)	P*
Plaque rupture	9	2	0·003
Intraplaque haemorrhage	9	7	0·2
Necrosis	10	10	0·4
Cap thinning in more than one cross-section	9	2	0·003

*Fisher's exact test

Discussion

The link between inflammation, COX and prostaglandins has been recognized for many years[24] although their potential role in atherosclerosis has only become apparent recently. The Physicians Health Study[25] reported a significant reduction in cardiovascular complications with aspirin therapy (325 mg every other day), and this was seen among those with a raised serum C-reactive protein level, a non-specific marker of inflammation. This finding suggested that the beneficial effects of aspirin may not be limited to its antiplatelet activity and that its anti-inflammatory actions via COX inhibition may also be important. However, aspirin is principally a COX-1 inhibitor[26] although recent studies assessing COX expression in normal and atherosclerotic arteries have highlighted the differential expression of COX-2 in atherosclerosis[20–22].

Previous reports, while confirming COX-1 and COX-2 expression in atherosclerotic arteries, have not assessed the expression of the two isoenzymes with respect to plaque instability and symptoms. This study demonstrated that both COX-1 and COX-2 were present in greater amounts in recently symptomatic carotid plaques and that expression was maximal, and significantly greater, in the collagen cap and shoulder regions of the plaque, close to the site of rupture. Further, there was a significant association between thinning of the collagen cap and plaque rupture with symptoms (*Table 2*). Also the localization of both COX isoforms to macrophages, endothelial cells and VSMCs was confirmed[21]. These findings, in conjunction with those of *in vitro* studies by Corcoran *et al.*[13] and Fitzsimmons *et al.*[15], which showed that stimulated macrophages expressed metalloproteinases (collagen lysis) and inhibited both synthesis and release of VSMC collagen via PGE_2-dependent pathways, suggest an important role for COX-1 and COX-2 in causing disruption of atherosclerotic plaques.

Nevertheless, the pattern of COX-2 staining differed from that of COX-1 in so much as it was also greater in the sclerotic region of symptomatic plaques. The predominant cellular component of the sclerotic region is VSMCs and it may be pertinent that COX-2 promotes VSMC proliferation and migration, both of which are the major contributors to the initiation and progression of atherosclerosis[27,28].

It is relevant to note that all patients from whom plaques were obtained for this study were on low-dose aspirin (75–150 mg daily). None was using other non-steroidal anti-inflammatory drugs or steroids. Previous studies have shown that low-dose aspirin inhibits only platelet COX-1 activity and has no effect on tissue (plaque) levels[29]. Previous studies have also shown that COX inhibitors only influence enzyme activity, without affecting COX messenger RNA and protein expression[30]. Thus COX expression seen in these plaques is unlikely to have been influenced by COX inhibitor drugs.

It is generally believed that COX-2, the inducible isoform, is responsible for pathological states, while the constitutive form, COX-1, has only physiological 'house keeping' functions. It was therefore surprising to find that COX-1 expression was increased in a similar way to COX-2. Support for the inducibility of COX-1 has recently emerged from several other studies. A clinical study investigating the functional contribution of COX-1 and COX-2 to increased PGI_2 synthesis in atherosclerosis found that both isoforms had a role[31]. In addition, *in vitro* work on liver macrophages[32], animal studies[33,34], human studies on prostate cancer[35], and studies using COX-1 and COX-2 gene knockout mice[36,37], have provided evidence for a constitutive and pathogenic role for both COX isoforms. Thus, selective inhibition of COX-2 may not produce the maximum therapeutic benefit.

Although this study relies on an immunohistochemical technique to quantify the expression of COX proteins, potential inaccuracies were minimized by using a standard protocol and a fixed colour detection threshold during computerized planimetry. This ensured objectivity and consistency in the determination of the percentage area of positive staining between the groups. The differences between the two groups were so great that other quantitative methods (e.g. Western blot, polymerase chain reaction) would almost certainly have confirmed these differences.

It could be argued that some of the asymptomatic patients in this study may have been classified incorrectly since they were not assessed for silent cerebral infarction. None the less, the Asymptomatic Carotid Atherosclerosis Study investigators[38] reported a frequency of 15 per cent for silent infarcts on computed tomography with only 28 per cent being cortical and thus possibly embolic. These silent infarcts were distributed evenly in both cerebral hemispheres with no correlation to the side of the asymptomatic stenosis, so casting doubt on the relevance of emboli to their pathogenesis. It is therefore unlikely that patients in this study were incorrectly defined as asymptomatic.

It might also be argued that increased levels of COX protein are the consequence and not the cause of plaque instability and rupture. Comparative cross-sectional studies such as this cannot answer this question. However, if the results of the present study are taken in conjunction with those from the *in vitro* work with macrophages and the Physicians Health Study, the case for a causative role is strong. Further support is drawn from the present results that indicate a significantly greater detection of COX-1 and COX-2 protein in the cap and shoulder (compared with the sclerotic regions) of plaques from asymptomatic patients (*Fig. 7*). Since routine histopathology demonstrated that plaques from this group of patients were characterized by thick, intact caps (*Table 2*), it would appear that increased expression of the COX isoforms in the cap and shoulder regions is evident before rupture.

It could also be argued that the association between the expression of COX-1 and COX-2 and the development of neurological symptoms suggests, but does not prove, functional relevance as regards plaque behaviour. This can only be determined by longitudinal studies that assess the effect of specific COX-1 and COX-2 inhibitors on known molecular markers of plaque instability.

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Portsmouth POSSUM models for abdominal aortic aneurysm surgery

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Background: The Portsmouth Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (P-POSSUM) equation permits comparative audit that allows for differences in case mix. The methodology has previously been shown accurately to model general surgical and vascular surgical patients. Patients with a ruptured abdominal aortic aneurysm (AAA) are, however, very different from elective patients and it may be hypothesized that they require their own specific risk model.

Methods: POSSUM data on 444 (213 emergency, 231 elective) admissions for AAA surgery between August 1993 and July 2000 were analysed using the P-POSSUM equation for general surgery and the P-POSSUM equations developed for vascular surgery.

Results: All equations successfully modelled the elective aneurysms but failed to fit the emergency aneurysms, and the elective and emergency aneurysms combined. This suggested that admission method (not a POSSUM data item) is an important factor for patients with AAA. However, with these data it was not possible to generate a model, including admission method, that successfully modelled the combined elective and emergency data. The 213 emergency aneurysm repairs were divided into two groups by operation date. The first 106 (training set) were used to form logistic regression models following the P-POSSUM methodology. These models were found successfully to fit the remaining 107 records (test set) on prospective application ($\chi^2 = 4{\cdot}50$, 4 d.f., $P = 0{\cdot}345$).

Conclusion: Ruptured AAAs appear to be different from elective AAAs and other vascular cases and require their own risk model.

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Introduction

The ability to audit surgical activity and outcome has become increasingly important in recent years. Crude contrast of morbidity and mortality data between populations does not allow for differences in case mix. Interest has focused on the development of audit systems that standardize patient data to allow meaningful comparison.

The Portsmouth Physiological and Operative Severity Score for enUmeration of Morbidity and mortality (P-POSSUM)[1] was developed as a modification of the original POSSUM equation described by Copeland *et al.*[2], which was shown to overestimate mortality. P-POSSUM was initially shown to provide an accurate method of comparative audit in a large series of general surgical patients[1]. Subsequently two further models based on the P-POSSUM methodology (physiological and operative, and physiology only) were developed and applied to an audit of operative outcome conducted by the Vascular Surgical Society of Great Britain and Ireland (VSSGBI). These V-POSSUM equations accurately predicted both mortality and morbidity after arterial surgery[3,4].

It was hypothesized that specific models may be required to evaluate certain operative procedures. In particular, it was a surprise how well the models could predict death in patients undergoing both elective and emergency abdominal aortic aneurysm (AAA) repairs. It is well established that surgery for ruptured AAA carries a much greater risk of death than elective surgery. The aim of this study therefore was to apply the P-POSSUM and V-POSSUM equations to all elective and emergency aneurysm operations in Portsmouth between August 1993 and July 2000. In the event that these models did not fit all patients with an aneurysm, a second aim was to generate a further model by logistic regression that would.

Table 1a V-POSSUM physiology and operative score model applied to all 444 patients with an abdominal aortic aneurysm (elective and ruptured)

Range of predicted mortality rate (%)	Mean predicted risk of death (%)	No. of operations	Predicted deaths	Reported deaths	χ^2
> 0 to ≤ 7	4·19	164	7	10	1·48
> 7 to ≤ 15	10·84	119	13	22	7·21
> 15 to ≤ 30	21·91	77	17	28	9·41
> 30 to ≤ 100	49·04	84	41	41	0·00
> 0 to ≤ 100	17·53	444	78	101	18·09

χ^2 = 18·09, 4 d.f., P = 0·012, evidence of significant lack of fit. This table demonstrates that the V-POSSUM model does not fit the group as a whole

Table 1b V-POSSUM physiology and operative score model applied to the 231 elective abdominal aortic aneurysm operations

Range of predicted mortality rate (%)	Mean predicted risk of death (%)	No. of operations	Predicted deaths	Reported deaths	χ^2
> 0 to ≤ 7	4·12	139	6	7	0·30
> 7 to ≤ 15	10·45	69	7	5	0·76
> 15 to ≤ 30	21·60	17	4	3	0·16
> 30 to ≤ 100	34·64	6	2	1	0·86
0 to ≤ 100	8·09	231	19	16	2·07

χ^2 = 2·07, 4 d.f., P = 0·725, no evidence of lack of fit. This table demonstrates that the V-POSSUM model gives a good fit, and can predict outcome after elective abdominal aortic aneurysm repair

Table 1c V-POSSUM physiology and operative score model applied to the 213 emergency abdominal aortic aneurysm operations

Range of predicted mortality rate (%)	Mean predicted risk of death (%)	No. of operations	Predicted deaths	Reported deaths	χ^2
> 0 to ≤ 7	4·63	25	1	3	3·07
> 7 to ≤ 15	11·38	50	6	17	25·38
> 15 to ≤ 30	22·00	60	13	25	13·53
> 30 to ≤ 100	50·15	78	39	40	0·04
0 to ≤ 100	27·78	213	59	85	42·02

χ^2 = 42·02, 4 d.f., P = 0, evidence of lack of fit. This table demonstrates that the V-POSSUM model does not predict outcome after emergency abdominal aortic aneurysm repair

Patients and methods

Data on all patients undergoing AAA surgery between August 1993 and July 2000 were extracted from the Portsmouth POSSUM database[1]. This contains POSSUM data on all admissions to the general surgery service since August 1993. A structured clerking and operation pro forma had been used to collect all the physiological and operative data items required to generate a POSSUM score for each patient[5]. During this interval 444 patients (213 emergency, 231 elective) underwent AAA repair. Six of the emergency admissions presented with an intact, symptomatic AAA; all the rest were ruptured. A vascular surgeon performed the majority of the procedures; a non-vascular consultant or surgical trainee was the principal surgeon in 14 elective and 63 emergency repairs. Patients who presented with a ruptured AAA and had no surgical intervention were not included in the study, as POSSUM requires an operative severity score. Mortality data presented herein are therefore in-hospital operative figures.

The P-POSSUM and V-POSSUM equations were applied to the elective and emergency AAA repairs and tested for goodness of fit. Statistical analysis was performed as described previously following the Hosmer–Lemeshow methodology[6–9]. This includes the use of the χ^2 test to compare frequency tables obtained from prospective application of the equations. It should be noted that this is

Table 2a P-POSSUM emergency abdominal aortic aneurysm model training set (physiology and operative scores)

Range of predicted mortality rate (%)	Mean predicted risk of death (%)	No. of operations	Predicted deaths	Reported deaths
> 0 to ≤ 30	20·85	31	6	5
> 30 to ≤ 45	38·16	33	13	14
> 45 to ≤ 60	50·96	21	11	11
> 60 to ≤ 100	67·83	21	14	14
> 0 to ≤ 100	41·51	106	44	44

Hosmer–Lemeshow χ^2 = 5·01, 8 d.f., P = 0·345, no evidence of lack of fit. This table demonstrates that it is possible to produce a model, based on P-POSSUM physiology and operative data, that predicts outcome after emergency abdominal aortic aneurysm repair

Table 2b P-POSSUM emergency abdominal aortic aneurysm model applied prospectively to test set (physiology and operative scores)

Range of predicted mortality rate (%)	Mean predicted risk of death (%)	No. of operations	Predicted deaths	Reported deaths	χ^2
> 0 to ≤ 30	23·58	24	6	8	1·27
> 30 to ≤ 45	37·89	45	17	16	0·10
> 45 to ≤ 60	51·45	23	12	8	2·56
> 60 to ≤ 100	68·99	15	10	9	0·57
> 0 to ≤ 100	41·95	107	45	41	4·50

χ^2 = 4·50, 4 d.f., P = 0·345, no evidence of lack of fit. This table demonstrates that the P-POSSUM emergency abdominal aortic aneurysm (AAA) model is a good model when applied prospectively to a subsequent group of patients having emergency AAA repair

a null hypothesis test: $P < 0·05$ indicates a significant lack of fit. While it is possible to say that a model is wrong (i.e. did not predict outcome), it is not possible to state that a different model is correct, only that it performed adequately. The risk ranges in the following tables were chosen to include approximately equal numbers of predicted deaths for each risk range, and to include greater than 5 percentage points where possible.

Results

Table 1a shows the results of prospective application of the V-POSSUM physiology and operative score model to all patients undergoing AAA repair. Lack of fit (i.e. failure of prediction) was found for this and both the V-POSSUM physiology-only model and the P-POSSUM model for general surgery[1] (data not shown). *Table 1b* gives the results of prospective application of the V-POSSUM physiology and operative score model to the elective AAA repairs only, with good prediction. Similarly successful fits were found for both the V-POSSUM physiology-only model and the P-POSSUM model for general surgery[1] (data not shown). *Table 1c* shows the results of the prospective application of the V-POSSUM physiology and operative score model to the ruptured AAA repairs only, with failure of prediction. Again, this lack of fit was repeated for both the V-POSSUM physiology-only model and the P-POSSUM model for general surgery[1] (data not shown).

Given that existing models could successfully describe elective AAA repair but failed to predict outcome after emergency AAA repair it seemed a reasonable hypothesis that mode of admission, which is not a POSSUM data item, should be included in the model. The Portsmouth POSSUM database includes mode of admission and it was simple to build models including mode of admission following the procedure used in the VSSGBI study[3,4]. However, it was not possible to develop a single, unified model (including mode of admission or otherwise) that successfully described outcome after both elective and emergency AAA repair.

Predictive model for ruptured abdominal aortic aneurysm

Since adequate models already existed for elective AAAs it was decided to attempt to develop a model to describe ruptured AAAs. The 213 ruptured AAA data records were divided into two to give a training set of 106, on which logistic regression was performed using SPSS statistical software (SPSS, Chicago, Illinois, USA) to obtain the

Table 3a P-POSSUM emergency abdominal aortic aneurysm model training set (physiology-only score)

Range of predicted mortality rate (%)	Mean predicted risk of death (%)	No. of operations	Predicted deaths	Reported deaths
> 0 to ≤ 30	25·33	32	8	6
> 30 to ≤ 45	37·92	37	14	17
> 45 to ≤ 60	53·86	23	12	12
> 60 to ≤ 100	67·47	14	9	9
> 0 to ≤ 100	41·48	106	44	44

Hosmer–Lemeshow $\chi^2 = 11{\cdot}81$, 8 d.f., $P = 0{\cdot}107$, no evidence of lack of fit. This table demonstrates that it is possible to produce a model, based only on P-POSSUM physiology data, that predicts outcome after emergency abdominal aortic aneurysm repair

Table 3b P-POSSUM emergency abdominal aortic aneurysm model applied prospectively to test set (physiology-only score)

Range of predicted mortality rate (%)	Mean predicted risk of death (%)	No. of operations	Predicted deaths	Reported deaths	χ^2
> 0 to ≤ 30	25·32	26	7	9	1·19
> 30 to ≤ 45	36·73	49	18	21	0·79
> 45 to ≤ 60	52·34	22	12	5	7·74
> 60 to ≤ 100	68·12	10	7	6	0·30
> 0 to ≤ 100	40·10	107	43	41	10·02

$\chi^2 = 10{\cdot}02$, 4 d.f., $P = 0{\cdot}040$, evidence of lack of fit. This table demonstrates that the P-POSSUM emergency abdominal aortic aneurysm model (physiology only) did not predict outcome accurately when applied prospectively to a subsequent group of emergency abdominal aortic aneurysm repairs. It did, however, come quite close, only overpredicting deaths in the predicted mortality range >45 to ≤ 60 per cent

following predictor equations. These equations were then applied prospectively to the test set of 107 patients. Two equations were developed; the first included both physiological and operative scores:

$$\text{In}(R/(1 - R) = -4{\cdot}9795 + (0{\cdot}0913 \times \text{physiological score}) + (0{\cdot}0958 \times \text{operative severity score})$$

where R is the risk of death. The second equation included only the physiological score:

$$\text{In}(R/(1 - R) = -2{\cdot}7569 + (0{\cdot}0968 \times \text{physiological score})$$

where R is the risk of death.

Table 2a, which is shown to allow comparison, demonstrates the application of equation 1 against its training set. The Hosmer–Lemeshow statistics given were produced by the SPSS statistics package used to generate the equation. There is no evidence of significant lack of fit. Prospective application of equation 1 against the test set of 107 emergency AAA repairs shows that the model successfully describes the data, and can therefore predict outcome (*Table 2b*).

Table 3a shows the application of the physiology-only model, equation 2, against its training set. The Hosmer–Lemeshow statistics indicate no evidence of significant lack of fit. Here, however, the prospective application of equation 2 against the test set reveals that the model performs badly in the 45–60 per cent risk range; the *P* value falls just below 0·05 indicating evidence of significant lack of fit, and failure of accurate prediction (*Table 3b*).

Discussion

The increased interest in surgical outcome has highlighted the need for accurate comparative audit that allows for differences in case mix. P-POSSUM methodology has been used to develop models specifically for vascular patients[3]. In general surgical patients[10] and in vascular patients the preoperative physiology score alone is predictive of death and major morbidity.

The current study has focused on patients who underwent AAA repair. The P-POSSUM and two V-POSSUM equations (physiological and operative, and physiology only) all successfully predicted mortality after elective surgery. These models, however, failed to fit emergency AAA repair. This implies that the mode of admission is important; however, even when it was included in the logistic regression, it was not possible to obtain a single, unified model that successfully described surgical mortality after both elective and ruptured aneurysm repair. The mode of admission is not the determining factor, rather the underlying disease process coincidentally determines the mode of admission. POSSUM was designed to look at all general surgery patients together. It is not surprising that focusing on a specific disease state renders factors particular to that condition more important, or alternatively, that a separate and distinct predictive model may be required. In the present study, using the P-POSSUM methodology, it was possible to model mortality after ruptured aneurysm surgery, but the model obtained was quite distinct.

The previously described POSSUM models have been demonstrated to predict outcome after a variety of arterial operations as reported in the National Audit Outcome of the VSSGBI[4]. Interestingly in this multicentre study 21·1 per cent of the 1476 patients had AAA surgery. A recent study applied the P-POSSUM methodology to a group of 153 patients undergoing elective conventional and endovascular AAA repair[11]. The equation accurately predicted mortality in both groups and predicted the previously described[12] high mortality rate after conventional aortic surgery. The P-POSSUM methodology therefore appears a robust method of predicting death not only in Portsmouth, but also in other geographical locations and in a large multicentre study of vascular patients.

It is of little surprise that ruptured aneurysms did not fit the previously developed P-POSSUM models. Reported mortality rates approach or exceed 50 per cent in many centres[13]. This is in comparison to elective mortality rates of approximately 5 per cent[14]. However, the present study has shown that outcome of ruptured AAAs can be modelled successfully. For ruptured aneurysms, with this data set, it was not possible to produce a physiology-only model that successfully predicted death in the test set (although it was successful when applied to the training set). It is possible that a larger data set may resolve this. Alternatively, perhaps in this case, where the physiology is being driven to an endpoint, the skill of a surgeon becomes more important than ever.

POSSUM is principally an audit tool. However, the physiology-only model potentially allows the surgeon to predict risk in an individual patient before surgery. A previous study identified a number of factors present on admission that were associated with 30-day mortality in patients undergoing surgery for ruptured AAA[15]. Five 'Hardman criteria' were associated with death; these were later applied to another retrospective series and validated this model[16]. The five criteria were age (over 76 years), serum creatinine (more than 190 mol/l), haemoglobin (less than 9 g/dl), loss of consciousness and electrocardiographic evidence of ischaemia. In the presence of three or more of these factors the outcome was universally fatal. These factors are very similar to some of those used by P-POSSUM to generate a physiology score. It is not a primary aim of P-POSSUM to predict death in an individual patient, but by generating a physiology-only score this is potentially possible. Although the physiology-only model generated for emergency AAA repair did not quite fit when applied prospectively (*Table 3b*), it came close, only overpredicting death in one predicted mortality range. It would certainly be worth applying this physiology-only equation to a larger group of operations as the relatively small numbers may have influenced this result.

One potential weakness of P-POSSUM mortality data for emergency AAA repair is that, by definition, it includes only patients who underwent surgery. In other words patients that were not offered surgery are excluded. This highlights the importance of patient selection for emergency aneurysm repair and may potentially limit the value of P-POSSUM in comparing mortality rates between different hospitals. P-POSSUM does allow stratification of risk, and therefore it is possible to identify whether a particular vascular unit is operating on a large or small proportion of high-risk patients.

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Performance indicators from routine hospital data: death following aortic surgery as a potential measure of quality of care

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Background: There is increasing pressure to monitor surgical performance. In the UK, the Department of Health has produced clinical indicators based on routine data to monitor performance. This study analysed whether such data could measure performance in aortic surgery.

Methods: Routine hospital data on postoperative mortality were collected for 1995–1997 in the Trent region. Procedural and diagnostic codes, modes of admission, districts of residence, treatment and specialty data were compared with audit data and the Operating Theatre Information System.

Results: Inaccuracies in the Health Resource Group (HRG) codes meant that 21·4 per cent of elective aortic cases (HRG Q02) were probably emergencies and 26 per cent of probable ruptured aneurysms were not coded as a vascular emergency. Case mix and patient selection introduced a bias, apparent between tertiary and district general hospitals. For patients aged over 80 years, two district hospitals undertook no elective aortic surgery; the rate for emergency aortic surgery varied between 16 and 25 per cent in the district hospitals, and was 77 per cent in the tertiary centre.

Conclusion: Crude mortality rates used as an indicator of performance are subject to bias and distortion owing to the collection of incorrect information, variation in patient selection between hospitals and case-mix differences. There was a considerable variation in selection and outcomes of patients undergoing aortic surgery in this study.

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Introduction

There is increasing pressure to monitor performance. Clinical governance is a Department of Health initiative designed to improve quality of care by improving the standard of clinical practice in the UK[1].

One proposed method of measuring performance is to use easily accessible and routinely collected hospital data. Mortality figures are a potential measure of outcome but they are useful only for comparatively common categories of admission, with a high expected mortality rate. One such example is aortic surgery. There are considerable concerns, however, about the use of routine data for this purpose[2]. Doubts have been raised about data accuracy, case-mix comparability and forms of selection such as cross-boundary referral. As part of a larger study[3] to consider issues surrounding the organization of vascular surgical services, an analysis has been conducted using routine data from a single health region, to look at the effects of these potentially distorting factors on overall mortality rates. A number of methods that might be used to improve the overall value of routine data were explored.

Materials and methods

Data analysis was carried out using standard anonymized data from the Trent region database over two financial years from 1995 to 1997. There were approximately 30 000 inpatient episodes related to vascular services. Data fields included procedural and diagnostic codes, mode of admission, district of residence, treatment and specialty. Record linkage was carried out using a concatenation of postcode and date of birth in order to identify patients transferred between hospitals.

For the detailed analysis the six districts of North Trent were used, comprising a single teaching hospital and five surrounding district general hospitals. Within each hospital data were compared with available clinical audit data or information from the Operating Theatre Information System. Specific issues that were addressed in the data

Table 1 Admissions for abdominal aortic aneurysm or aortic surgery

	Admissions (per 100 000 population per year)		
	Suprarenal AAA*	Aortic – elective	Aortic – emergency
Barnsley	1·77 (0·54 to 2·99)	8·33 (5·67 to 10·99)	5·08 (3·00 to 7·16)
Doncaster	0·34 (– 0·13 to 0·81)	8·97 (6·56 to 11·39)	5·89 (3·93 to 7·84)
North Derbyshire	1·19 (0·41 to 1·97)	9·76 (7·53 to 11·99)	6·80 (4·94 to 8·66)
North Nottinghamshire	1·02 (– 0·35 to 2·39)	7·52 (3·81 to 11·23)	9·83 (5·59 to 14·07)
Rotherham	0·78 (0·02 to 1·54)	5·99 (3·87 to 8·11)	8·29 (5·80 to 10·78)
Sheffield	0·57 (0·11 to 1·02)	6·38 (4·85 to 7·90)	6·34 (4·82 to 7·86)
Total	0·98 (0·66 to 1·31)	7·68 (6·78 to 8·59)	7·27 (6·38 to 8·15)

Values in parentheses are 95 per cent confidence intervals. *These values are based on district of residence not district of treatment. AAA, abdominal aortic aneurysm

analysis included the consistency of coding, identification of indicators of patient selection, case-mix differences and selection through cross-boundary flow.

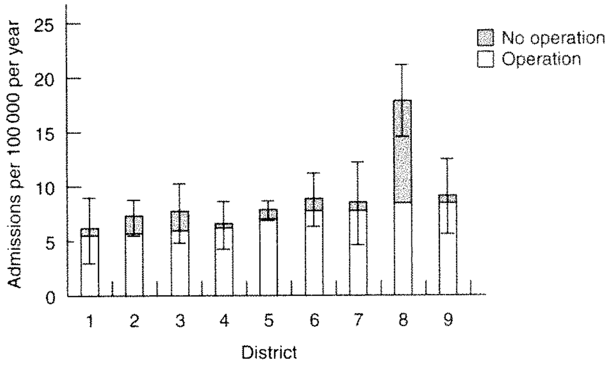
Results

Admission rates

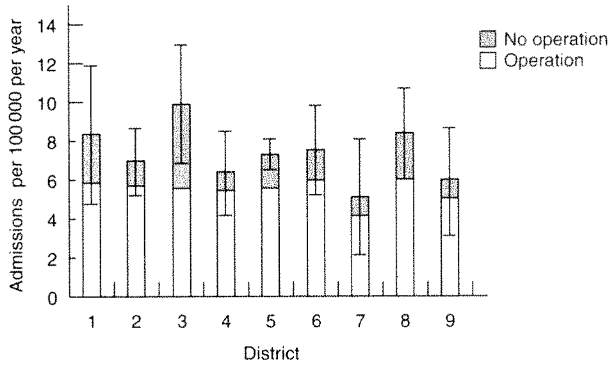
All admissions in which there was a procedural code related to an abdominal aortic procedure irrespective of specialty, or a diagnostic code of abdominal aortic aneurysm (1713 or 1714) combined with the speciality of general or vascular surgery, were identified. These were then subdivided into a complex group, in which one code identified suprarenal and visceral vessel surgery, and codes for all other vascular cases, which were divided based on mode of admission to hospital. The overall admission rates for these categories of patients within each district in Trent are shown in *Table 1*. *Fig. 1* shows elective and emergency admissions further subdivided to show the proportion with a coded aortic procedure in the same admission.

Coding accuracy

Using procedure codes from the Office of Population Censuses and Surveys (OPCS)[4] and the International Classification of Diseases, tenth revision (ICD10) coding systems[5], Healthcare Resource Group (HRG) codes were derived[6]. This has defined two groups that may relate to aortic surgery: emergency aortic surgical procedures (Q01) and elective abdominal vascular surgical procedures (Q02). The correlation between these and the listed mode of admission to hospital is shown in *Table 2*. Inaccuracies in the HRG coding meant that 21·4 per cent of elective aortic cases were actually emergencies.



a Elective aortic admissions



b Emergency aortic admissions

Fig. 1 Rates of admission and procedures for all districts within Trent for **a** elective and **b** emergency admissions. Districts (anonymized) are in ascending order of total rates of elective aortic surgery. Error bars represent 95 per cent confidence intervals of total

In one hospital that had local audit data available, it was found that 10 per cent of patients who underwent emergency aortic surgery were misclassified on the basis

Table 2 Relationship between emergency and elective admissions, and procedural codes for patients undergoing aortic procedures

	Elective admission	Emergency admission
Emergency procedure	6·8	93·2
Elective procedure	78·6	21·4

Values are percentages

of the primary procedural code as an elective patient. Twenty-six per cent of patients classified as having an emergency aortic operation on the basis of diagnostic codes would not have a vascular surgical code under HRG definitions. This subgroup of patients had no procedural code that could connect them to a ruptured abdominal aortic aneurysm. There was either no procedure code listed or a non-specific code such as T309 – unspecified opening of abdomen, L912 – insertion of central venous catheter, and X501 – DC cardioversion. This group of patients had a mortality rate in excess of 80 per cent.

Case-mix selection

Within North Trent, elective suprarenal aortic surgery and visceral vessel procedures were carried out only in a single (teaching) hospital.

There was considerable variability in case mix. One example is patient age; 28 per cent of the total emergency admissions in the region comprised patients aged over 80 years. Some 77 per cent of those over the age of 80 years received surgery in the teaching hospital while only 16–25 per cent underwent surgery in the district hospitals. For elective surgery a mean of 6 per cent of total admissions were patients aged over 80 years. Two district hospitals undertook no elective surgery on patients over the age of 80 years, whereas 11 per cent of elective operations at the teaching hospital were for patients in this age group.

Outcome

The crude in-hospital mortality rate for the teaching hospital was half that of the combined rate for the other hospitals (*Table 3*). The in-hospital mortality rate for the teaching hospital was subdivided according to whether patients were local or tertiary referrals from the surrounding districts (*Table 4*). This showed evidence of selection with differences in mortality rate. Out-of-district elective admissions had a higher operative mortality rate than local admissions, whereas the converse was true for emergency admissions.

Table 3 In-hospital mortality rates following aortic surgery in the teaching hospital and surrounding district hospitals

	Mortality rate (%)	
	Teaching hospital	Surrounding district hospitals
Elective	4·2 (0·9–7·4)	10·5 (5·5–15·5)
Emergency	30·4 (22·3–38·5)	59·4 (49·8–69·0)
Emergency (including no operation)	35·1 (27·0–43·2)	75·4 (68·9–82·0)

Values in parentheses are 95 confidence intervals

Table 4 In-hospital mortality rates following aortic surgery in the teaching hospital for local patients and tertiary referrals from surrounding districts

	Mortality rate (%)	
	Local	Referrals
Elective	3·4	5·3
Emergency	33·8	25·0
Emergency (including no operation)	40·7	25·0

Discussion

These results highlight some of the problems that can lead to inaccuracies in routine data. Raw data may present a distorted view of outcomes for a number of reasons. Miscoding between emergency and elective aortic procedures is a significant problem. It arises because the HRG coding system relies on the accuracy of the OPCS coding, with emergency and elective aortic aneurysm procedures being coded in one of several possible ways. The large difference between the expected mortality rate for these two operations means that even a small percentage of miscoding can significantly affect the overall mortality rate. If the degree of miscoding between institutions is consistent then the figures would still remain comparable. However, this would be difficult to verify and would still include inaccuracies, which is unacceptable. A more consistent grouping may be obtained by coding initially into suprarenal or visceral vessel procedures, and infrarenal aortic procedures. The infrarenal aortic procedures can then be subdivided on the basis of method of admission to hospital[3].

Another source of bias comes from selection of patients for surgery. It can be seen that there is considerable variation in selection of patients for emergency aortic surgery. To allow for this all patients admitted to hospital with the relevant diagnosis must be accounted for rather than just those who undergo surgical repair.

The nature of the surgery carried out in specialist centres may also create differences. Specialist centres often undertake higher-risk procedures such as visceral vessel surgery and suprarenal aortic aneurysm repair. These carry a higher mortality rate and this factor needs to be acknowledged. The current HRG system combines high-risk operations with lower-risk procedures.

Patient selection is again in evidence when data for transfer of patients between hospitals are examined. These data suggest that patients local to the referral centre have a lower elective surgical risk but a higher emergency risk. This could be explained by the likely selection pattern of transferring complex elective (higher risk) patients to the tertiary centre but not the high-risk emergency patients who are less fit for transfer. An alternative explanation for the lower emergency mortality rate after transfer could be the occurrence of a significant number of deaths during transfer. However, no such events were recorded over this interval.

Even when taking these factors into account there remain significant differences in outcome between hospitals. This is in keeping with the mounting evidence that better outcomes can be obtained through subspecialization and centralization of surgical services[7].

Measurement of performance in the National Health Service (NHS) is under close scrutiny. This has had implications for clinical governance, audit, management and provision of services. Cardiac surgeons in the UK have had a surgical register since 1977, but recently it has become apparent that the data would have to be audited in a more explicit way[8]. The Society of Cardiothoracic Surgeons has since advocated collection of data that facilitates effective risk stratification.

In 1997 the Department of Health in the UK first published its intent to measure progress using a performance framework in a White Paper, *The New NHS*[9]. Performance indicators were suggested that could be derived from routinely collected data[10].

The relationship between case-mix and outcome data has been shown to be significant in several studies[11]. North American studies have shown that mortality rates are affected by the severity of illness, and by inaccurate or inappropriate data collection[12]. By taking into account the severity of illness the predicted mortality rate could vary by as much as eightfold[13]. Flawed data collection can have a huge impact in the outcome figures and so present an inaccurate reflection of performance.

Careful analysis of existing data regarding coding accuracy, case mix, patient selection and cross-boundary flow could improve their value. There is still a need for more detailed collection of data that include an indication of risk. Further improvement could involve the use of different coding systems such as Read codes[14] or by using scoring systems that allow for risk statistics based on case mix such as Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity[15,16].

Regardless of the problems inherent in using routine data, there is likely to be increasing availability and use of such data to monitor performance and quality. Careful consideration needs to be given to simple measures that could be taken to ensure that data are as accurate as possible. Likely confounding factors should be identified explicitly. The collection of high-quality data, which are useful as performance indicators, will depend on developing working practices, clinical coding systems and data sets that are designed specifically for such purposes.

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Original article

Clinicopathological factors predicting outcome after resection of mass-forming intrahepatic cholangiocarcinoma

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Background: The prognosis for patients with intrahepatic cholangiocarcinoma differs according to macroscopic type. The identification of clinical and pathological features that predict outcome in patients with mass-forming intrahepatic cholangiocarcinoma is required in order to determine optimal surgical strategies for patients with this type of tumour.

Methods: The details of 35 patients with resected mass-forming intrahepatic cholangiocarcinomas were analysed retrospectively. Univariate analysis of potential prognostic factors was performed.

Results: The cumulative survival rate at 1, 3 and 5 years after operation was 58, 33 and 33 per cent respectively. Patients with stage II tumours had a better outcome than those with advanced stage tumours. By univariate analysis, lymphatic invasion, lymph node metastasis, intrahepatic satellite lesions and microscopic resection margin involvement were found to be highly significant variables and were identified as possible risk factors for a poor outcome after operation.

Conclusion: When frozen-section examination of lymph nodes reveals negative nodal metastasis, extensive anatomical hepatic resection is indicated for mass-forming intrahepatic cholangiocarcinomas. Intraoperative frozen-section examination of the resection margin to confirm the absence of cancer cells is recommended.

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Introduction

Although curative surgical resection provides the only chance of long-term survival for patients with intrahepatic cholangiocarcinoma (ICC), the postoperative prognosis of ICC remains poor despite considerable progress in preoperative imaging, operative techniques and perioperative management[1–15].

The periductally infiltrating type of ICC originates from major ducts near the hepatic hilum and invades along the bile ducts, whereas the mass-forming type takes origin from a peripheral bile duct and invades adjacent liver parenchyma directly[16]. As Ki-*ras* gene alterations have been linked to periductally infiltrating ICC but not to mass-forming ICC, mechanisms of carcinogenesis and underlying tumour behaviour may differ between the mass-forming and periductally infiltrating types[17]. Therefore, surgical strategy should be individualized for each macroscopic type in order to improve the postoperative outcome[1–6]. In the present study various clinicopathological features were investigated as possible prognostic factors for outcome following surgery for the mass-forming type of ICC, with a view to determining the best surgical strategy for this type of tumour.

Patients and methods

Between January 1983 and December 1999, hepatic resection was performed in 820 patients with primary liver cancer. Tumours included 757 hepatocellular carcinomas, 51 ICCs (representing 6·2 per cent of all tumours), eight mixed hepatocellular and bile duct carcinomas, and four cystadenocarcinomas. The 51 ICCs were classified by macroscopic appearance according to the system proposed by the Liver Cancer Study Group of Japan[18]. Fourteen patients had a periductally infiltrating type of tumour extending along the bile ducts. Two patients had intraductally growing tumours characterized by papillary growth within a bile duct lumen. Thirty-five patients with mass-forming tumours presented a nodular mass with a distinct border; the latter patients were analysed in this study.

Tumour stage was defined according to the pathological tumour node metastasis (pTNM) classification proposed by the Union Internacional Contra la Cancrum[19] (*Table 1*). The subsegments corresponded to segments in the classification of Couinaud[20]. Histological diagnoses were reviewed to identify prognostically significant factors. All resected specimens were cut into slices 5 mm thick and fixed in 10 per cent formalin. Paraffin-embedded tissues were stained with haematoxylin and eosin. The system of the Liver Cancer Study Group of Japan[18] as subsequently modified[16,21] was used to categorize histological findings. When clusters of cancer cells were present in the blood vessels (portal and/or hepatic vein) or lymphatic vessels, the tumour was considered to be positive for vascular or lymphatic invasion respectively. Perineural invasion was defined by the presence of tumour cells within or extending along perineural spaces. When multiple lesions were demonstrated, the largest nodule was identified as the principal tumour nodule, and others were defined as intrahepatic metastases. When the tumour-free margin of resection was less than 5 mm by histological examination, the margin was considered positive for tumour. Patient characteristics and clinicopathological features were analysed as variables possibly affecting prognosis.

Cumulative survival rates were calculated by means of the Kaplan–Meier method, and univariate survival differences were tested with the log rank test. Multivariate analysis using a Cox proportional hazard model could not be included in this series because of the small study size (23 deaths occurred in the series). While differences associated with a *P* value of less than 0·05 were deemed significant, false-negative errors should be considered because the number of patients in this retrospective study was insufficient. Moreover, multiple univariate tests were performed, which had a risk of reaching a false-positive conclusion.

Table 1 Tumour node metastasis pathological classification

Stage	Tumour	Node	Metastasis
I	T_1	N_0	M_0
II	T_2	N_0	M_0
IIIA	T_3	N_0	M_0
IIIB	T_1	N_1	M_0
	T_2	N_1	M_0
	T_3	N_1	M_0
IVA	T_4	Any N	M_0
IVB	Any T	Any N	M_1

T_1: solitary, 2 cm or less, without vascular invasion. T_2: solitary, 2 cm or less, with vascular invasion; multiple, one lobe, 2 cm or less, without vascular invasion; solitary, greater than 2 cm, without vascular invasion. T_3: solitary, greater than 2 cm, with vascular invasion; multiple, one lobe, 2 cm or less, with vascular invasion; multiple, one lobe, greater than 2 cm, with or without vascular invasion. T_4: multiple, more than one lobe; invasion of major branch of portal or hepatic veins; invasion of adjacent organs other than gallbladder; perforation of visceral peritoneum. N_1: regional lymph node metastasis. M_1: distant metastasis

Results

Patient characteristics

The 35 patients comprised 24 men and 11 women, with a mean age of 61 (range 35–83) years. The most common symptom was right upper quadrant abdominal pain (15 patients); others were weight loss (nine), fever (five), generalized fatigue (four) and jaundice (two). Twelve patients were asymptomatic. Serum hepatitis B surface antigen (HBsAg) was tested in 32 patients; three were positive for HBsAg. Of these 32 patients, 24 patients had hepatitis C virus serology, of whom five were positive. Serum concentrations of carcinoembryonic antigen exceeded the reference range (greater than 6·5 ng/ml) in 15 patients. Of 28 patients whose serum was tested for carbohydrate antigen 19-9, 22 had concentrations exceeding the reference range (greater than 37 ng/ml).

Surgical procedures

Hepatic resections included two left trisegmentectomies, two right trisegmentectomies, two extended right bisegmentectomies, eight extended left bisegmentectomies, five right bisegmentectomies, nine left bisegmentectomies, one central bisegmentectomy, two anterior segmentectomies, one lateral segmentectomy, one posterior segmentectomy and two limited hepatic resections. Resection included the caudate lobe in 11 patients in whom the right or left hepatic duct was suspected to be involved based on observations either before or during operation. Lymph node dissection, including the hepatoduodenal ligament, the area surrounding the common hepatic artery and the retropancreatic region, was performed in 23 patients; nine of these also underwent para-aortic lymph node dissection. Five patients had lymph node dissection including only the hepatoduodenal ligament. The remaining seven patients underwent hepatectomy without lymph node dissection, either because the preoperative diagnosis was incorrect (hepatocellular carcinoma or hepatolithiasis) or because macroscopic lymph node metastasis was not suspected on the basis of intraoperative findings. Although 20 patients proved at operation to have bile duct invasion, this was suspected before surgery in only 11. Resection of the extrahepatic bile duct and biliary reconstruction with Roux-en-Y hepaticojejunostomy was required to perform curative surgery in seven patients with bile duct invasion. Frozen-section examination of the resected bile duct stump was performed to confirm tumour-free resection margins in three patients. One patient underwent a wedge resection of the stomach because of direct tumour invasion. Resection and reconstruction of the right hepatic artery was performed in two patients. Four patients underwent a partial resection of the inferior vena cava with primary repair.

Clinicopathological characteristics

There were ten patients with a stage II tumour, eight with stage IIIA, six with stage IIIB and 11 with stage IVA tumours. Tumour diameter ranged from 2·0 to 16·0 (mean 7·0) cm. Twenty-one tumours were located in the left hepatic lobe, with 14 in the right lobe. Fifteen patients had multiple tumours, which were distributed in bilateral hepatic lobes in four patients. Except for one well differentiated tubular adenocarcinoma, 26 and eight tumours were categorized as moderately and poorly differentiated tubular adenocarcinoma respectively. Vascular, perineural and lymphatic invasion was present in 17, 13 and 21 patients respectively. Lymph node metastasis was confirmed histologically in 16 patients. Although curative resection histologically free of tumour at the margin itself was achieved in 28 of 35 patients, only 12 of the 28 patients had resection margins that remained tumour-free for more than 5 mm. Histological examination of resected specimens revealed tumour cells within 5 mm of resection margins in 12 of 15 patients with multiple tumours, and in nine of 13 with a main tumour size exceeding 7 cm.

Outcome after operation

The median length of survival after hepatectomy for mass-forming ICC was 436 days. The survival rate of 35 patients at 1, 3 and 5 years after operation was 58, 33 and 33 per cent respectively (*Fig. 1*). Thirteen postoperative complications included six liver abscesses and six bile leaks. Three operative deaths occurred from postoperative sepsis following cholangitis. Sixteen other patients died from cholangitis or hepatic failure due to intrahepatic recurrence, which occurred in the remnant liver either at the surgical stump or in the segment adjacent to the primary lesion. Among 16 patients developing intrahepatic recurrence, 13 did not have tumour-free margins that exceeded 5 mm. Three deaths resulted from multiple pulmonary recurrences, and the remaining patient with a fatal outcome died from gastrointestinal bleeding secondary to direct invasion of the stomach by disseminated tumour.

Median survival time was 395 days for patients with a stage IIIA tumour, 304 days for those with a stage IIIB tumour and 128 days for stage IVA tumours. In contrast, the 5-year survival rate in patients with a stage II tumour was 86 per cent (*Table 2*). Patients with stage II tumours had a significantly better outcome than those with stage III or IV tumours ($P < 0.001$). Lymphatic invasion ($P < 0.001$), lymph node metastasis ($P < 0.001$), multiple lesions

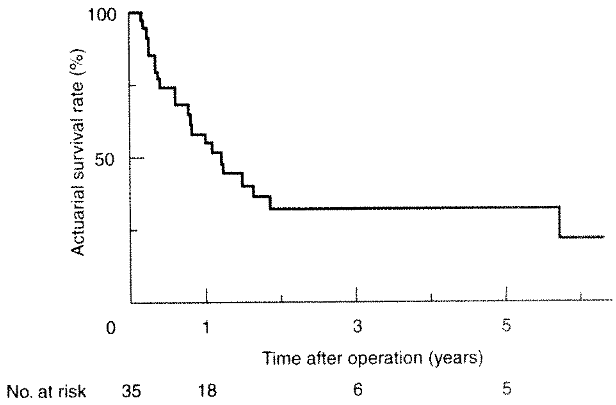

Fig. 1 Overall survival of 35 patients after hepatic resection for mass-forming intrahepatic cholangiocarcinoma

Table 2 Median survival times and survival rates according to tumour node metastasis pathological stage

pTNM stage	*n*	Median survival (days)	Cumulative survival rate (%) 1 year	3 years	5 years	*P**
II	10	–	100	86 (60–100)	86 (60–100)	< 0·001
III or IV	25	293	43 (23–62)	14 (0–29)	—	
IIIA	8	395	63 (29–96)	31 (0–66)	—	
IIIB	6	304	50 (10–90)	—	—	
IVA	11	128	24 (0–51)	0	0	

Values in parentheses are 95 per cent confidence intervals. pTNM, pathological tumour node metastasis. *Log rank test

(P = 0·0015) and a microscopically involved resection margin (P < 0·001) were found to be highly significant and were identified as possible predictors of prognosis after operation (*Tables 3* and *4*).

Discussion

Although patients with intrahepatic cholangiocarcinoma usually have a poor prognosis after operation, previous series[7,8] have indicated that they have a chance of long-term survival when the resected tumour is classified as stage I or II. In the present series postoperative survival in patients with stage II tumours was also much longer than that of those with advanced stage tumours. This series analysed various clinicopathological features including components of the tumour staging schema, and identified potential risk factors of resected ICC in order to determine a surgical strategy for patients with this tumour.

Various factors including tumour size and microscopic invasion, specifically vascular and lymphatic invasion, have been identified as significant prognostic factors in patients with ICC[1–13]. Additionally, some authors have recommended that ICC should be classified into mass-forming and periductally infiltrating types for better planning of surgical strategy, as various characteristics (pathological features, patterns of recurrence and prognosis after operation) differ between patients with mass-forming tumours and those with periductally infiltrating tumours[1–6].

Previous studies have suggested that complete resection with lymph node dissection may improve long-term survival because lymph node metastasis is significantly associated with poor outcome[6–13]. Other studies have advocated hepatic resection without lymph node dissection for mass-forming tumours because lymph nodes involved by mass-forming tumours are less common than with periductally infiltrating tumours[1,2]. However, Inoue *et al.*[3] reported that 21 of 52 patients with mass-forming ICCs had lymph node metastases, which significantly decreased the overall survival. In this series, 16 patients among 35 with mass-forming tumours had lymph node metastases. Sixteen patients underwent lymph node dissection for nodal metastasis. None the less, 15 of these 16 patients died within 2 years of operation. The therapeutic effectiveness, extent and indication of lymph node dissection for patients with lymph node metastasis could not be identified, although examination of lymph nodes for metastases is useful for estimating prognosis. On the other hand, the outcome was better in patients without lymph node metastasis than in those with nodal metastases. When negative lymph node metastasis is revealed by frozen-section examination, extensive anatomical resection should be performed.

Table 3 Details of patients with mass-forming intrahepatic cholangiocarcinoma: univariate analysis with respect to outcome

	No. of patients	Cumulative survival rate (%)			
		1 year	3 years	5 years	*P*
Age (years)					
< 60	14	47 (19–71)	23 (0–50)	23 (0–50)	0·23
⩾ 60	21	66 (45–86)	38 (15–60)	38 (15–60)	
Sex					
M	24	53 (33–73)	31 (11–52)	31 (11–52)	0·67
F	11	73 (46–99)	36 (4–68)	—	
Symptoms					
Asymptomatic	12	64 (36–92)	51 (19–83)	—	0·20
Symptomatic	23	56 (35–76)	25 (6–44)	25 (6–44)	
HBsAg*					
Positive	3	100	50 (0–100)	50 (0–100)	0·29
Negative	29	56 (37–75)	29 (11–48)	29 (11–48)	
HCVAb*					
Positive	5	61 (38–84)	27 (5–49)	—	0·67
Negative	19	80 (45–100)	—	—	
CEA					
Raised	15	47 (21–72)	12 (0–32)	—	0·03
Normal	20	67 (45–89)	47 (23–72)	47 (23–72)	
CA19-9*					
Raised	22	56 (33–78)	33 (9–57)	33 (9–57)	0·50
Normal	6	67 (29–100)	17 (0–46)	—	

Values in parentheses are 95 per cent confidence intervals. *Hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCVAb) and serum carbohydrate antigen (CA) 19-9 levels were measured before operation in 31, 24 and 28 patients respectively. CEA, carcinoembryonic antigen

Although previous studies reported the presence of multiple tumours to be an independent risk factor[8,9], another study suggested that if radical removal of the tumour is technically feasible and can be accomplished safely it should be performed even when multiple tumours are detected because the presence of intrahepatic metastases does not significantly influence the prognosis[3]. The indication for operation in patients with multiple tumours is still inconclusive. The detection of multiple tumours was identified as a possible predictor of worse survival in this series, in which four patients who had bilobar multiple tumours died within 10 months of operation.

Some authors have reported that tumour involvement of the resection margin is an independent factor associated with a poor prognosis in patients with ICC[7,10]. Patients with a mass-forming tumour had a poor outcome when tumour cells were identified within 5 mm of the resection margin. Non-curative operations for ICC with histologically involved resection margins have represented 15–40 per cent of operations performed with curative intent in previous reports[4–13]. In the present series, non-curative operations found to show histologically demonstrable tumour cells at the resection margin itself accounted for only seven patients. However, among the remaining 28 patients histological examination revealed that 16 had tumour cells within 5 mm of the margin. In particular, 12 of 15 mass-forming tumours with multiple tumours and nine of 11 tumours greater than 7 cm in diameter proved to have a tumour-positive resection margin. Resection margin status is difficult to confirm macroscopically during operation, and clear margins are difficult to achieve. Intraoperative frozen-section examination of the margin should be performed to confirm the absence of cancer cells, especially in patients with multiple tumours or tumour size exceeding 7 cm.

Intrahepatic recurrence tended to occur in the remnant liver at the surgical stump or in the segment adjacent to the primary lesion. Therefore, when no lymph node metastasis

Table 4 Clinicopathological details of patients with mass-forming intrahepatic cholangiocarcinoma: univariate analysis with respect to outcome

	No. of patients	Cumulative survival rate (%)			*P*
		1 year	3 years	5 years	
Tumour size (cm)					
< 7	22	67 (47–87)	44 (21–69)	44 (21–69)	0·03
≥ 7	13	43 (15–71)	11 (0–30)	—	
Location of main tumour					
Right lobe	14	56 (30–83)	45 (16–74)	45 (16–74)	0·92
Left lobe	21	60 (38–81)	27 (7–47)	27 (7–47)	
Differentiation					
Poor	8	38 (4–71)	0	0	0·08
Well or moderate	27	57 (37–76)	42 (21–62)	42 (21–62)	
Vascular invasion					
Present	17	41 (18–65)	14 (0–31)	—	0·01
Absent	18	76 (56–97)	52 (26–79)	52 (26–79)	
Perineural invasion					
Present	13	53 (25–80)	11 (0–30)	11 (0–30)	0·12
Absent	22	63 (42–83)	46 (24–68)	46 (24–68)	
Lymphatic invasion					
Present	21	38 (17–59)	11 (0–25)	—	< 0·001
Absent	14	91 (74–100)	70 (41–99)	70 (41–99)	
Bile duct invasion					
Present	20	42 (20–65)	12 (0–28)	12 (0–28)	0·01
Absent	15	71 (47–95)	63 (37–89)	42 (4–80)	
Lymph node metastasis					
Present	16	25 (4–46)	—	—	< 0·001
Absent	19	90 (75–100)	60 (34–85)	60 (34–85)	
No. of tumours					
Multiple	15	34 (10–59)	0	0	0·0015
Single	20	79 (60–97)	60 (36–83)	60 (36–83)	
Resection margin					
Involved by tumour	23	40 (24–66)	—	—	< 0·001
Free of tumour	12	92 (76–100)	71 (44–99)	71 (44–99)	

Values in parentheses are 95 per cent confidence intervals is revealed by lymph node frozen-section examination, extensive anatomical resection is required to accomplish cure. Intraoperative frozen-section examination of the margin to confirm the absence of cancer cells is recommended, especially when the mass-forming ICC is large or has produced intrahepatic metastases.

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Original article

Late mortality in patients with severe acute pancreatitis

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Background: Mortality due to severe or necrotizing acute pancreatitis most often results from multiorgan dysfunction syndrome (MODS) occurring either early (within the first 14 days) or 2 weeks or more after the onset of symptoms due to septic complications. The aim of this study was to analyse the course of the disease in patients who died from severe acute pancreatitis.

Methods: Between January 1994 and August 2000 details of 263 consecutive patients with acute pancreatitis were entered prospectively into a database. All patients were treated in an intermediate or intensive care unit.

Results: The overall mortality rate was 4 per cent (ten of 263 patients). The mortality rate was 9 per cent (ten of 106) in patients with necrotizing disease. No patient died within the first 2 weeks of disease onset. The median day of death was 91 (range 15–209). Six patients died from septic MODS. Ranson score, Acute Physiology and Chronic Health Evaluation (APACHE) II score during the first week of disease, pre-existing co-morbidity, body mass index, infection and extent of necrosis were significantly associated with death ($P < 0{\cdot}01$ for all parameters). However, only infection of the necrotic pancreas was an independent risk factor in the multivariate analysis.

Conclusion: Early deaths in patients with severe acute pancreatitis are rare, mainly as a result of modern intensive care treatment. Nine of the ten deaths occurred more than 3 weeks after disease onset. Infection of pancreatic necrosis was the main risk factor for death.

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Introduction

Over the past decade it has become clear that acute severe pancreatitis progresses in two phases. The first 14 days are characterized by a systemic inflammatory response syndrome (SIRS) due to the release of various mediators[1–3]. Currently, two peaks in mortality can be seen during the course of severe acute pancreatitis[4]. Patients who die early (within the first 14 days) usually do so as a result of a massive SIRS without apparent infection[5]. Later, death most often results from septic multiorgan dysfunction syndrome (MODS) caused by secondary infection of pancreatic or peripancreatic necrosis. A previous study investigated microbiological findings in patients with necrotizing pancreatitis and found the occurrence of multiresistant organisms to be a rare finding and fungal infection not to be associated with a negative outcome[6].

The aim of this study was to analyse the course of the disease in patients suffering from severe acute pancreatitis and to compare non-survivors with survivors.

Patients and methods

Between January 1994 and August 2000, 263 patients with acute pancreatitis were treated at the Department of Visceral and Transplantation Surgery at Berne's University Hospital. Of these patients, according to the Atlanta classification[7], 156 suffered from mild disease and 107 from severe disease. With respect to morphology, 157 patients had oedematous pancreatitis and 106 had necrotizing pancreatitis. Mortality in patients with either mild or oedematous disease was zero; therefore, only patients with necrotizing pancreatitis were studied.

Necrotizing pancreatitis was defined as the appearance of pancreatic and/or extrapancreatic necrosis[8] on contrast-enhanced computed tomography (CT)[9] together with a serum C-reactive protein (CRP) level of more than 150 mg/l. CT was performed within 96 h of admission and repeated weekly in patients whose clinical condition did not improve. A treatment strategy based on infection of the nectrotic pancreas has been published previously[10]. Clinical and laboratory severity staging of acute pancreatitis was

Table 1 Definitions of pre-existing co-morbidity

1	Pulmonary: chronic obstructive pulmonary disease (World Health Organization definition)
2	Cardiac insufficiency class 3 or 4 (according to New York Heart Association)
3	Renal: serum creatinine level greater than 250 µmol/l or need for haemofiltration or haemodialysis
4	Liver disease: cirrhosis Child–Pugh class A, B or C
5	Metabolic disease: diabetes mellitus (type I or II)
6	Malignant disease diagnosed within 5 years of current episode
7	Immunological disease or chronic immunosuppressive medication

carried out using Ranson's prognostic signs[11], the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system[12] and determination of serum CRP levels. After admission patients were cared for in an intermediate or intensive care unit. Routine antibiotic treatment (imipenem–cilastatin) was given soon (4 h or less) after CT findings of necrosis. CT-guided fine-needle aspiration (FNA) was carried out if infection of necrosis was suspected clinically. Newly developed signs of metabolic disorders and deterioration of organ failure of lung, kidney or the cardiocirculatory system as defined in the Atlanta classification[7] and/or clinical signs of sepsis[13] were reasons for FNA. Infection of pancreatic necrosis as proven by FNA was regarded as an indication for surgical treatment and resulted in operative intervention within 24 h. With few exceptions, patients without signs of pancreatic infection were treated without operation.

Endoscopic retrograde cholangiopancreatography (ERCP) was performed in cases of biliary aetiology and a papillotomy was done if stones or sludge were present in the common bile duct.

Co-morbidity was defined as a pre-existing disease or condition in addition to the current disease. Co-morbidity was diagnosed if the condition was considered an active problem before acute pancreatitis became the 'principal disease'. Definitions of co-morbidity as used in this study are given in *Table 1*.

Statistical analysis

All data were collected prospectively and entered into a statistical program, Statistical Package for the Social Sciences, version 10·0 (SPSS, Chicago, Illinois, USA). For univariate analysis variables were analysed with Fisher's exact test or the Mann–Whitney *U* test. Thereafter parameters were entered in a multivariate analysis. $P < 0{\cdot}05$ was considered statistically significant. Receiver–operator characteristic (ROC) curve analysis was performed for body mass values, APACHE II and Ranson scores.

Results

One hundred and six patients were staged as having necrotizing pancreatitis according to CT findings and were included in the study. The aetiology of acute pancreatitis was biliary in 48 patients (45 per cent) and alcohol overindulgence in 37 (35 per cent); another or an undefined aetiology was found in 21 patients (20 per cent). There was no difference in age, sex or aetiology between survivors and non-survivors.

The overall mortality rate in patients with severe pancreatitis was 9 per cent (ten of 106). The mortality rate in patients with sterile necrosis was 3 per cent (two of 72), compared with 24 per cent (eight of 34) in patients with infected necrosis ($P < 0{\cdot}01$). *Fig. 1* summarizes the mortality in patients with necrotizing pancreatitis grouped according to status of infection and treatment modality.

Patients died after a median of 91 (range 15–209) days. No patient died within the first 2 weeks of onset of symptoms. The earliest death occurred on day 15 in a patient in whom FNA proved infection on the same day. Surgery was not performed because of rapid clinical deterioration.

Organ failure was diagnosed a median of 3 (range 1–26) days after the onset of symptoms. In eight of the ten patients who died, organ failure became apparent during the first 5 days of the disease. However, organ failure also occurred in 70 survivors ($P = 0{\cdot}14$).

In seven of the ten patients who died, infectious sequelae were the primary cause of death. In one of these patients sudden death was due to septic pulmonary emboli, confirmed on autopsy. Two patients died from cardiac arrest and one from severe adult respiratory distress syndrome.

Thirty-two patients with infected necrosis and three with sterile necrosis were treated by means of operation, of whom six and one died respectively (*Fig. 1*). All patients who came to operation either still showed or again showed evidence of organ failure. In the majority of these patients organ failure was caused by pancreatic infection. In three patients with sterile necrosis, surgery was performed because of persisting organ failure despite maximum intensive care treatment.

Univariate analysis revealed that maximum APACHE II score during the first week, Ranson score, pre-existing co-morbidity, necrosis of more than 50 per cent of the gland, infection of necrosis and body mass index (BMI) were negative risk factors (*Table 2*).

ROC curve analysis revealed a sensitivity of 78 per cent and a specificity of 80 per cent of a Ranson score greater than 5 for predicting a fatal outcome (area under the curve 0·84 (95 per cent confidence interval (c.i.) 0·73–0·92)). An

APACHE II score greater than 10 had a sensitivity of 70 per cent and a specificity of 62 per cent for predicting death (area under the curve 0·75 (95 per cent c.i. 0·65–0·83)) and a BMI greater than 30 kg/m^2 showed a sensitivity of 70 per cent and a specificity of 83 per cent for predicting a fatal outcome (area under the curve 0·79 (95 per cent c.i. 0·68–0·88)).

Several other clinical and biochemical parameters were also investigated, including organ failure, fever greater than 39°C, maximum CRP level, serum calcium level less than 2 mmol/l, serum albumin concentration lower than 30 g/l, blood glucose level above 11 mmol/l (in the absence of diabetes mellitus), lactate dehydrogenase level greater than 600 units/l, total white blood count, duration of parenteral nutrition and delay of enteral feeding. In addition, in patients treated by surgery, the length of operation, need for blood transfusion, diverting ileostomy and timing of operation (delay in days after onset of symptoms) were investigated. None of these parameters correlated with outcome. All parameters with $P < 0·05$ were then subjected to a multivariate analysis with a stepwise forward regression. Infection of necrosis was the only parameter investigated that proved to be an independent risk factor for death (*Table 2*).

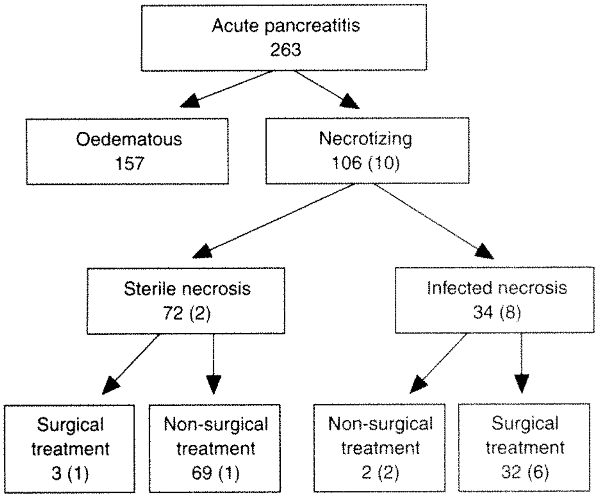

Fig. 1 Patients with necrotizing pancreatitis grouped according to status of infection and treatment modality. Values in parentheses indicate the number of patients who died in each group

Discussion

According to recent guidelines edited by the British Society of Gastroenterology, the mortality rate today for acute pancreatitis should be lower than 10 per cent overall and less than 30 per cent in patients diagnosed with severe disease[4]. The mortality rate in the present series for those with severe disease was 9 per cent, and ranged from 3 to 24 per cent depending on infection status and treatment modality.

Death in patients with acute pancreatitis depends on several factors. Patients at high risk are those who develop a severe SIRS, those with infected necrosis and elderly patients with co-morbid medical problems[4]. However, the patterns of mortality and morbidity in acute pancreatitis have changed over time. Others have reported a considerable proportion of patients dying early as a result of a severe SIRS causing MODS[14–20]. Renner *et al.*[18] analysed 405 deaths from acute pancreatitis retrospectively: 60 per cent died within 1 week of admission and lung pathology was predominant. Similarly, in a review of 126 deaths from acute pancreatitis between 1974 and 1984, the time to death was less than 1 week in the majority of patients[19]. In a large tertiary-care hospital in the USA, approximately half of the deaths occurred within the first 14 days[14]. In contrast, early deaths did not occur at all in the present study. This raises the question as to whether all patients with acute pancreatitis were included or whether any subgroup of patients was admitted to another service. The University Hospital of Berne is a tertiary referral centre, and patients with severe disease are cared for in the intensive care unit.

Table 2 Clinical and biochemical parameters that correlated with mortality

	Survivors (n = 96)	Non-survivors (n = 10)	P	
			Univariate	Multivariate
Extent of necrosis greater than 50 per cent	29	9	< 0·001	0·51
BMI (kg/m^2)*	25(5·2)	33·5(7)	< 0·01	0·28
Infection of necrotic pancreas	26	8	< 0·01	0·016
Pre-existing co-morbidity	24	7	< 0·01	0·62
APACHE II score during the first week of illness*	9·4(4·2)	13·6(4·7)	< 0·05	0·8
Ranson score*	3·6(2·1)	6·4(1·6)	< 0·05	0·2

*Values are mean(s.e.m.). APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index

All patients in whom the diagnosis 'acute pancreatitis' was established, regardless of age or co-morbidity, were included in the study. Nevertheless, there is the theoretical possibility that in individual patients the treating physician may have decided not to pursue any diagnostic or therapeutic interventions. Because autopsies are not performed routinely in Switzerland, the number of such patients remains unknown. On the other hand, it is important to bear in mind the present data regarding time point of organ failure and severity scores in both survivors and non-survivors, indicating that patients with severe disease were included in this series. Toh *et al.*[21] audited the process and outcome of management of patients with acute pancreatitis against the UK guidelines. Importantly, in severe cases, there was poor use of objective severity stratification (19 per cent), low admission rates to a high-dependency unit or intensive care unit (67 per cent) and only 33 per cent of patients had CT. Similarly, in a prospective multicentre audit, Mann *et al.*[16] reported that only 44 per cent of their patients with a pre-mortem diagnosis of acute pancreatitis had undergone CT. In the present study, the aggressive early severity staging allowed for early initiation of intensive care treatment in patients with severe disease and might have been one reason for survival during early SIRS. Death occurred after a median of 91 days despite the fact that the first organ failure was diagnosed a median of 3 days after onset of the disease. Accordingly, Ranson and APACHE II scores calculated during the first 48 h and first week respectively showed higher values for non-survivors than for survivors. These scores, as well as the Imrie score, which was not calculated in this series, have proven to be the best predictors of severity, a complicated course of the disease and death[22,23]. However, while they function well for identification of groups of patients, they are only moderately accurate for individual patients. Indeed, for a cut-off level of 5 Ranson and 10 APACHE II points, the sensitivity for predicting a negative outcome did not exceed 78 and 70 per cent respectively, and the specificity did not exceed 80 and 62 per cent.

In this study, aetiology (gallstones, alcohol, other or unknown causes) had no influence on outcome, suggesting that, once the pathogenic mechanisms have initiated the disease, the course and outcome of acute pancreatitis are not influenced by underlying aetiological factors. Some authors have published similar results[35], while Lankisch *et al.*[36] reported that alcohol-induced pancreatitis is more often associated with necrosis than other aetiologies and that patients with alcohol-induced pancreatitis more frequently need artificial ventilation. Fung *et al.*[37] analysed a group of 72 patients, in six of whom pancreatitis was induced by ERCP, and concluded that acute pancreatitis was more severe, but not associated with an increased mortality rate, when it was ERCP induced.

The statistical analysis revealed 'extent of necrosis' as a risk factor for a negative outcome. However, it has to be kept in mind that the extent of necrosis is a risk factor for infection of the necrotic tissue, and infection is another determinant of the outcome. Previous work showed that necrosis by itself (i.e. sterile necrosis), even when involving more than 50 per cent of the gland, was associated with a better outcome compared with infected necrosis[10]. Accordingly, it was recently shown that in patients with sterile necrosis the extent of necrosis correlated with the frequency of organ failure, whereas infected necrosis was associated with organ failure irrespective of the extent of necrosis, supporting the concept of infection being the major determinant of outcome[24]. However, the issue of sterile necrosis continues to be controversial[10,25–29].

Pre-existing co-morbidity was also found to be correlated with a fatal outcome. Taking into account that five of the present patient deaths occurred more than 95 days after disease onset and these patients spent at least 2 months in intensive care, this result is not surprising because pre-existing morbidity is an indicator for reduced functional reserves of different organ systems.

In addition, a high BMI was found to be a negative prognostic factor, as has been described previously[30–32]. In contrast, in a group of 320 patients with acute pancreatitis, obesity did not carry an increased risk of developing organ failure or fatal outcome[33]. In an earlier study looking at obesity, it was an independent predictor of respiratory failure but was not a predictor of renal failure, pancreatic necrosis or need for operation[34].

Multivariate analysis found only 'infection of necrosis' to be an independent risk factor for death. Several factors may contribute to this finding. There was a considerable numerical difference between non-survivors and survivors. Because patients died late after disease onset, there was a long interval during which an individual patient might improve or deteriorate, decreasing the importance of the initially documented disease severity.

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Original article

Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases

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Background: The purpose of this study was to investigate whether adjuvant therapy can improve survival after curative resection of colorectal liver metastases.

Methods: Some 235 patients had 256 liver resections for metastatic colorectal cancer. There were no predefined criteria for resectability with regard either to the number or size of the tumours or to locoregional invasion, except that resection had potentially to be complete and macroscopically curative. All patients who had curative hepatic resection were advised to start postoperative adjuvant chemotherapy.

Results: The resectability rate in screened patients was 91 per cent (235 of 259 patients); the postoperative mortality rate was 4 per cent. In 35 patients resection of the primary tumour was performed simultaneously with partial liver resection. Forty-four patients (19 per cent) developed intra-abdominal recurrence; 14 (6 per cent) underwent reoperation and the recurrent tumour was resected. Adjuvant chemotherapy was given to 99 patients (55 per cent), most treatments being based on 5-fluorouracil with folinic acid. The overall actuarial survival rates at 1, 3 and 5 years were 87, 60 and 36 per cent respectively. In a multivariate analysis, four or more metastases, preoperative carcinoembryonic antigen level higher than 5 ng/ml and a positive resection margin were independent predictors of poor outcome. Adjuvant chemotherapy improved the 5-year survival rate to 53 per cent.

Conclusion: This study provides some evidence that postoperative chemotherapy is beneficial; however, prospective randomized studies are necessary to define its exact role.

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Introduction

Hepatic resection is the only potentially curative treatment option available for patients with metastases from colorectal carcinoma limited to the liver[1]. However, tumour relapse occurs in up to 60 per cent of patients who undergo resection[2–5]. Several large series have reported a 25–40 per cent long-term survival rate after curative resection of hepatic metastases, whereas the rate without therapy is less than 2 per cent[1,6].

Previous studies of hepatic resection for liver metastases have focused on prognostic factors. The main purpose of this article is to provide criteria for excluding patients with poor characteristics before operation[2–5,7–12]. As surgery is the only current therapy with potential for cure, efforts should not be directed simply at restricting potential candidates for operation, but also at improving the results of liver resection with adjuvant therapy.

In patients with colorectal cancer and tumour invasion of regional lymph nodes, adjuvant chemotherapy after resection of the primary tumour reduces the risk of death by 30 per cent[13,14]. Palliative chemotherapy of liver metastases from colorectal cancer produces an objective response in about 20–30 per cent of patients[8,15]. Hepatic arterial chemotherapy has increased the clinical response rate, but its use is limited by severe complications and no overall long-term survival benefit has been demonstrated[8,16]. No prospective study completed to date has assessed the value of adjuvant systemic chemotherapy after hepatic resection of metastatic colorectal cancer[5,9–11,16].

The purpose of this study was to investigate whether systemic adjuvant chemotherapy could improve the survival of patients with liver metastases after liver resection.

Patients and methods

Between January 1991 and September 2000, 235 patients had 256 liver resections for metastatic colorectal cancer in a tertiary referral centre. All patients had histologically confirmed colorectal adenocarcinoma with resectable hepatic metastases.

Selection criteria for liver resection included medical fitness for major surgery with no sign of disseminated disease on preoperative imaging. There were no predefined criteria with regard to either the number or size of the tumours or to locoregional invasion, except that resection should potentially be complete and macroscopically curative. The preoperative imaging studies were abdominal computed tomography (CT) and arterial portography until September 1996, when dual-phase (portal and equilibrium) helical CT was used. Details of the technique and results have been reported previously[17]. Disseminated disease was ruled out by CT of the chest and pelvis. Colonoscopy was repeated if a normal recent examination was not available. The histopathological report of the primary tumour was reviewed in order to confirm that the first resection was complete. Biochemical profile included blood count, measurement of serum levels of transaminase, cholinesterase, carcinoembryonic antigen (CEA) and CA-19·9 tumour markers, and blood coagulation. Radiographic studies were reviewed at a twice-weekly multidisciplinary meeting and surgical resection was scheduled if considered appropriate. All patients gave written informed consent to undergo operation.

Patients with a primary tumour and synchronous hepatic metastases were considered for partial colectomy and hepatic resection. When liver metastases were associated with pulmonary metastases and both were resectable, the policy was first to perform the liver resection followed, after two or three courses of chemotherapy, by the pulmonary resection. At laparotomy, all patients underwent thorough exploration before hepatic resection. The extent of the hepatic disease was assessed by intraoperative ultrasonography and bimanual palpation to confirm the number and size of metastases, to define their relationship with intrahepatic vascular structures, and to look for occult liver metastases. All operations were performed in the same hospital under the direct supervision of the same surgeon.

All patients who underwent curative hepatic resection were advised to start postoperative adjuvant chemotherapy. Systemic chemotherapy was initiated 4 weeks after resection, and six cycles were scheduled. 5-Fluorouracil (5-FU) was administered daily for 5 days as an intravenous bolus of 425 mg per m^2 body surface area, preceded each day by an infusion of leucovorin at a dose of 200 mg/m^2. If a patient had previously received 5-FU and leucovorin, the systemic chemotherapy was administered as 5-FU in continuous infusion. In the last 12 patients other types of systemic chemotherapy such as irinotecan and oxaliplatin were allowed.

After the first liver resection, all patients were followed every 6 months with liver function tests, helical CT and estimation of CEA and CA-19·9 levels. Colonoscopy was performed every year. Repeat hepatectomy was considered if further liver recurrence was technically resectable and if helical CT of the chest, abdomen and pelvis revealed no irresectable extrahepatic disease. The resectability of recurrences in the lung was discussed with the thoracic surgeons. Any recurrences that were deemed operable were resected, including locoregional and anastomotic recurrences.

Demographic information, date of initial surgery, stage of the tumour, details of the postoperative course and history of postoperative adjuvant chemotherapy were entered prospectively into a computer database. Survival curves were calculated with the Kaplan–Meier method. Differences in survival times were compared with the log rank test. Multivariate analysis was carried out using the Cox proportional hazards model. The χ^2 test was used to compare frequencies. To ensure that all patients analysed had the opportunity to complete 6 months of postoperative chemotherapy, postoperative deaths and patients who survived for less than 6 months were excluded from the survival analysis with adjuvant chemotherapy.

Results

Patient characteristics

The mean(s.e.m.) age of the 235 patients was 61(10) years; there were more men than women (61 *versus* 39 per cent). In 82 patients (35 per cent), liver metastases were discovered synchronously with a primary tumour; in 35 of these, resection of the primary tumour and partial liver resection were performed simultaneously. Some 113 patients (48 per cent) had a solitary liver metastasis, but in 51 patients (22 per cent) there were four or more. The mean(s.e.m.) number of metastases was 2·3(1·9) (range 1–12) per patient. Subsequent pathological review of the liver resection specimen revealed positive surgical margins in 29 patients (12 per cent) (*Table 1*).

Table 1 Kaplan–Meier univariate analysis of prognostic factors for survival after resection of colorectal liver metastases in 235 patients

	No. of patients	No. alive	Actuarial survival, months (%)				Log rank
			12	24	36	60	
Metastases							
≥ 4	51 (22)	30 (59)	80	52	35	23	0·004
< 4	184 (78)	134 (73)	89	78	51	40	
No. of lobes involved							
Bilobar	78 (33)	51 (65)	85	63	41	19	0·01
One lobe	157 (67)	113 (72)	88	79	68	44	
CEA (ng/ml)							
< 5	71 (32)	58 (82)	88	84	79	63	0·03
> 5	153 (68)	101 (66)	86	69	54	29	
Extrahepatic disease							
Yes	36 (15)	21 (58)	90	57	43	0	0·03
No	199 (85)	143 (72)	88	75	66	45	
Positive margin							
Yes	29 (12)	20 (69)	73	64	0	0	0·01
No	206 (88)	148 (72)	90	75	64	38	
Adjuvant chemotherapy*							
Yes	99 (55)	80 (81)	97	87	80	53	0·0008
No	81 (45)	44 (54)	88	66	48	25	

Values in parentheses are percentages. *Calculated with 180 patients. CEA, carcinoembryonic antigen

Extrahepatic disease

In this study, 36 patients with extrahepatic disease underwent liver resection. Twelve patients had recurrence at the site of primary tumour resection, eight had direct involvement of the diaphragm by extension of the tumour, three had positive portal lymph nodes, three had localized peritoneal involvement and ten had lung metastases noted before operation. Liver resection was performed at the same time as partial colectomy in eight patients, with lymphadenectomy of mesenteric lymph nodes in four, resection of the diaphragm in eight, resection of a localized peritoneal recurrence in three and lymphadenectomy of portal nodal disease in three patients. In two patients with simultaneous pulmonary metastases, partial lung resection could not be performed because of poor general condition and postoperative complications.

Resection rate

Some 309 patients with liver metastases from colorectal cancer were referred for possible surgical treatment of liver metastases during the study interval. Fifty were deemed unsuitable for hepatic resection because of advanced tumour or irresectable extrahepatic disease on preoperative helical CT. The remaining 259 patients had laparotomy with curative intent but 24 had irresectable disease: ten had peritoneal carcinomatosis, five had irresectable extrahepatic disease and nine irresectable metastases. The resection rate of patients considered suitable for surgery was 91 per cent (235 of 259).

Perioperative results

Within 30 days of operation, nine patients (4 per cent) had died, from acute myocardial infarction, urinary sepsis, liver failure (two patients), peritonitis after anastomotic leakage, pulmonary embolism, pneumonia (two) or stroke. The median postoperative hospital stay was 10 (range 5–58) days. One hundred and sixty resections (63 per cent) were followed by an uneventful recovery without morbidity. Biliary fistula was the most common postoperative complication (23 patients; 9 per cent), followed by wound infection in 22 patients (9 per cent), intra-abdominal abscess in 20 (8 per cent), pneumonia in five (2 per cent) and miscellaneous complications in 34 patients (13 per cent). In 145 operations (57 per cent) liver resection involved three or more segments (major liver resection). Preoperative blood donation was used in 121 patients (47 per cent). Only 23 per cent of patients required allogeneic blood transfusion (59 of 256 operations).

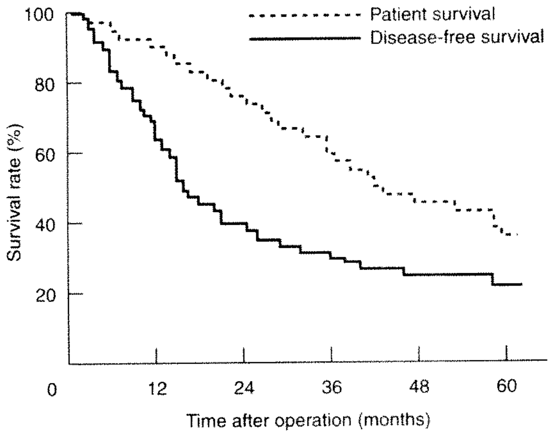
Postoperative chemotherapy

After resection of the liver metastases adjuvant chemotherapy was given to 99 patients (55 per cent) (*Table 1*). The

Table 2 Baseline characteristics of patients after hepatectomy according to treatment group

	Adjuvant chemotherapy (n = 99)	No treatment (n = 81)	P*
Mean(s.d.) age (years)	59(9)	62(10)	0·02
Metastases			
Synchronous	44 (44)	19 (23)	0·005
Metachronous	55 (56)	62 (77)	
No. of lobes involved			
Unilobar	70 (71)	53 (65)	0·52
Bilobar	29 (29)	28 (35)	
Extrahepatic disease			
Yes	14 (14)	11 (14)	1·0
No	85 (86)	70 (86)	
Positive margin			
Yes	8 (8)	9 (11)	0·6
No	91 (92)	72 (89)	
Previous treatment			
None	63 (64)	29 (36)	0·001
Adjuvant chemotherapy	36 (36)	52 (64)	
Simultaneous surgery	20 (20)	6 (7)	0·01

Values in parentheses are percentages. Patients with less than 6 months' follow-up were excluded. χ^2 test



No. at risk						
Patient	235	148	86	43	20	11
Disease-free	235	109	47	22	10	6

Fig. 1 Cumulative patient survival and overall disease-free survival of 235 patients after resection of colorectal liver metastases

remaining 81 did not receive postoperative chemotherapy for the following reasons: 29 declined, 30 had received 5-FU during the previous 3 months, seven were not considered appropriate for the protocol and 15 were excluded for miscellaneous reasons. Most treatments were based on 5-FU. Seventy-nine patients received intravenous 5-FU in combination with folinic acid; eight patients received 5-FU alone in continuous infusion, and five in combination with oxaliplatin. Seven patients received irinotecan.

On comparison of patients who did and those who did not have adjuvant chemotherapy after resection of liver metastases, there were no significant differences with respect to baseline characteristics, including sex, number of liver metastases, extrahepatic disease, Dukes' stage, preoperative CEA level, type of resection and number of positive margins. However, patients who had chemotherapy were younger, fewer had received previous chemotherapy, and more had synchronous metastases and simultaneous surgery of the primary tumour (*Table 2*).

Recurrence and long-term outcome

The median follow-up was 20 months. One hundred and nineteen patients (51 per cent) developed recurrence of the colorectal cancer. Hepatic recurrence was observed in 72 patients (31 per cent). A repeat hepatectomy could be performed in 21 patients. Pulmonary metastases developed before or after the liver resection in 60 patients (26 per cent); pulmonary resection could be performed in 17. Forty-four patients (19 per cent) developed intra-abdominal recurrence; 14 (6 per cent) underwent reoperation and the recurrent tumour was resected. In 91 patients the recurrences were multicentric.

The mean(s.e.m.) survival of 235 patients who had curative resection calculated from the time of liver resection was 51(4) months. The actuarial survival rate at 1, 3 and 5 years was 87, 60 and 36 per cent respectively (*Fig. 1*). The 1-, 3- and 5-year cumulative rate of overall recurrence was 37, 71 and 79 per cent respectively. Mean(s.e.m.) disease-free survival was 34(3) months.

Univariate predictors of long-term survival

Results of univariate analysis of prognostic factors after liver curative resection in 235 patients are summarized in *Table 1*. Multiple liver metastases were a predictor of poor outcome. Patients with bilobar disease, the presence of extrahepatic disease and preoperative CEA level greater than 5 ng/ml also had a poorer survival. Other pathological features of the metastases such as synchronous presentation and size of the principal tumour were not predictors of long-term outcome. The major surgical factor that influenced long-term outcome was clearance of tumour, determined by margin invasion at histological examination. No patient with a positive margin survived 3 years. However, no significant differences in outcome were found between patients who had simultaneous surgery of the primary tumour, intraoperative transfusion, repeated hepatectomy or resection of pulmonary metastases. Patients who had

Table 3 Multivariate analysis of prognostic factors of survival by Cox proportional hazards forward stepwise method

	ARR	*P*
≥ 4 metastatic nodes	2·6 (1·4–4·9)	0·002
Preoperative CEA level > 5 ng/ml	2·8 (1·3–6·0)	0·009
Positive resection margin	2·6 (1·1–6·8)	0·04
Adjuvant chemotherapy after hepatectomy	0·3 (0·2–0·6)	0·0003

Values in parentheses are 95 per cent confidence intervals. ARR, adjusted relative risk; CEA, carcinoembryonic antigen

adjuvant chemotherapy had a better 5-year survival rate than those who did not. Survival at 5 years was 53 per cent, compared with 25 per cent for patients who had no postoperative chemotherapy.

Multivariate analysis of survival

Multivariate analysis by the proportional hazard method was done using surgical clearance margin, number of tumours, type of metastases (synchronous *versus* metachronous), bilobar involvement, presence of extrahepatic disease, preoperative CEA level and the use of adjuvant chemotherapy after hepatectomy as co-variates. Four or more metastases, CEA level greater than 5 ng/ml, positive resection margin and adjuvant chemotherapy after liver resection were independent predictors of outcome (*Table 3*). Adjuvant chemotherapy had a protective effect, improving the prognosis, independent of the presence of more synchronous metastases and previous treatment with chemotherapy after resection of the colorectal cancer.

Discussion

Surgical resection of colorectal liver metastases is safe and effective[2–5,7–12]. The present study confirms the value of resection for hepatic metastases of colorectal cancer. However, up to 60 per cent of patients will relapse, either in the liver or elsewhere[5,7]. Many prognostic risk factors have been identified in retrospective studies of resection of colorectal liver metastases[3,5,7,9–12]. This study confirms the importance of some factors: the presence of four or more nodes, bilobar involvement, extrahepatic disease, preoperative CEA level and the value of clearance of the surgical margin (*Table 1*). Preoperative patient selection is advocated as the best way to improve the results of liver resection. However, given the lack of an alternative therapy, surgical resection could be considered in all patients, provided that all the disease is resectable and operative mortality and morbidity rates are acceptable.

In the present study systemic adjuvant chemotherapy was recommended to all patients after surgical resection. Patients who had adjuvant chemotherapy had a better 5-year survival rate than those who did not. Patients who had chemotherapy and those who did not were similar, except that patients who had chemotherapy were younger, a greater proportion had not had previous chemotherapy and more had synchronous liver metastases (*Table 2*). The presence of synchronous metastases is supposed to be an adverse characteristic and it cannot explain the better survival of the treated group. Previous exposure to 5-FU is one of the main reasons for reluctance to give further adjuvant chemotherapy after resection of liver metastases. In the present study, there were more patients having first-time chemotherapy in the treatment group. However, with the new drugs (oxaliplatin and irinotecan), postoperative chemotherapy could be administered to the last 12 patients who had previous chemotherapy with 5-FU. Multivariate analysis confirmed the protective effect of postoperative chemotherapy ($P = 0{\cdot}0003$). The mode of presentation of the metastases (synchronous) and previous exposure to 5-FU were not significant prognostic factors in the multivariate analysis, and thus were unrelated to the response to chemotherapy. The results of this study are similar to those of other studies that have demonstrated improved survival with chemotherapy after resection of metastases [11,16].

In a randomized controlled trial of surgery followed by hepatic arterial infusion of 5-FU and folinic acid, there was no improvement in survival, mainly due to the morbidity of the procedure and the toxic effects of intra-arterial chemotherapy[18]. In another recent randomized study, systemic chemotherapy given after resection of liver metastases was compared with combined systemic and hepatic arterial chemotherapy[19]. Combined chemotherapy improved survival at 2 years, but there was no control group to test the benefit of systemic chemotherapy alone.

Many studies of hepatic resection include only patients with fewer than four metastases, and without extrahepatic disease[3,10,11,18]. In the present study 22 per cent of the patients had four or more metastases and 15 per cent had extrahepatic disease. However, the 5-year survival rate of 36 per cent compares favourably with that of previous studies[2–5,7,9–12,18]. It may be argued that the resectability and survival rates were high in this study because of selection of only the best candidates for surgery. Yet the number of patients with metastases, more than four tumours, the presence of extrahepatic disease and bilobar involvement is one of the highest reported to date. Despite the presence of poor prognostic factors, the operative mortality rate in all the studies is lower than 5 per cent and the 5-year survival rate ranges between 28 and 38 per cent[3,5,7,12,20].

This study has provided some evidence that postoperative chemotherapy is beneficial. A prospective randomized study should be done to define the exact role of adjuvant systemic chemotherapy after resection of hepatic metastases.

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Gamma-glutamyl transpeptidase messenger RNA may serve as a diagnostic aid in hepatocellular carcinoma

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Introduction

Making an early diagnosis of hepatocellular carcinoma (HCC) is very important, in the hope that early treatment may be curative. Studies of γ-glutamyl transpeptidase (GGTP) messenger RNA (mRNA) in HCC strongly suggest that changes in hepatic GGTP expression may be closely related to the development of HCC[1–4]. Tsutsumi *et al.*[5] found that type A hepatic GGTP mRNA was expressed in livers of normal individuals and those with non-cancerous liver diseases, while type B was found in livers with HCC. The aim of the present study was to elucidate the patterns of GGTP expression in both cancerous and non-cancerous liver tissues and to explore any potential diagnostic role.

Patients and methods

Forty patients with HCC who underwent curative hepatectomy (functional division of the liver according to Couinaud's nomenclature) at Mackay Memorial Hospital, between January 1997 and June 1998, entered this study. Underlying diseases were hepatitis B in 30, hepatitis C in six, and both hepatitis B and C in two patients. No patient had alcoholism and two patients had neither hepatitis B nor C. Five healthy subjects, five patients with chronic active hepatitis (CAH) and five with cirrhosis who represented varying risk of HCC acted as a control to the disease group. There were four patients with hepatitis B and one patient with hepatitis C in each group of CAH and cirrhosis among the control patients.

The specific types of complementary DNA (cDNA) of GGTP mRNAs were examined in liver biopsies, and cancerous and non-cancerous tissues of patients with HCC. The prevalence of the types of GGTP cDNA in each condition was compared. Liver specimens were stored at – 80°C pending RNA extraction. χ^2 test or Fisher's exact test were used; $P < 0.05$ was considered as significant.

Results

All controls had type A and two controls had polygenic cDNA (type A + B in one patient with cirrhosis, type A + C in one patient with CAH) (*Table 1*). In the non-cancerous liver from patients with HCC, less type A (28 of 40; $P < 0.05$) and more type B (28 of 40; $P < 0.001$) was found than in controls. In cancerous tissue, less type A (ten of 40; $P < 0.001$ *versus* control, $P < 0.001$ *versus* non-cancerous tissue) and more type B (33 of 40; $P < 0.001$ *versus* control) was detected. A fair sensitivity (70 per cent), a good specificity (93 per cent) and a low false-positive rate (7 per cent) were found when using the presence of type B in liver to predict the risk of HCC development.

Discussion

These results support the observations of Tsutsumi *et al.*[5] that GGTP mRNA expression in the human liver may shift from type A to B during the development of HCC. The high prevalence of type B in non-cancerous tissues of livers with HCC suggests that the shift may occur in the preneoplastic stage. Furthermore, these data suggest a fair sensitivity and a good positive prediction of HCC from type B GGTP mRNA. Using a 16-G biopsy needle, 1 cm of liver tissue is enough for the study of GGTP mRNA. In cases in which HCC is suspected but imaging and pathological findings are controversial, detection of type B may suggest that the patient already has HCC or is at high risk of developing it. Further diagnostic evaluation or close follow-up would be warranted.

It is concluded that examination of type B GGTP mRNA may be a valuable aid in the diagnosis of HCC or its precancerous stages.

Table 1 Incidence of γ-glutamyl transpeptidase messenger RNA types in liver tissue

	Type of GGTP mRNA					
	A*	B†	A + B	All B	All A	Nil
Control (*n* = 15)	13	0	1	1	15‡	0
Patients (*n* = 40)						
Non-HCC	12§	12¶	16	28§	28¶	0
HCC	1§**	24§††	9	33§	10§**	6

GGTP mRNA, γ-glutamyl transpeptidase messenger RNA; HCC, hepatocellular carcinoma. *Monogenic for type A; †monogenic for type B; A + B, polygenic for type A and type B (‡one control was polygenic, type A + C). §$P < 0.001$, ¶$P = 0.024$ *versus* control; **$P < 0.001$, ††$P = 0.007$ *versus* non-HCC (χ^2 test or Fisher's exact test were used; $P < 0.05$ was considered as significant)

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Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer

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Background: Local recurrence of rectal cancer after curative resection remains a difficult clinical problem. The aim of this study was to elucidate prognostic risk factors after resection of recurrent cancer.

Methods: Between January 1983 and December 1999, 83 patients with locally recurrent rectal cancer were studied retrospectively for survival benefit by re-resection. Sixty patients underwent resection for recurrent cancer, including total pelvic exenteration in 30 patients and sacrectomy in 23 patients. The extent of locally recurrent tumour was classified by the pattern of pelvic invasion as follows: localized, sacral invasion and lateral invasion.

Results: Multivariate analysis showed that the pattern of pelvic invasion was a significant prognostic factor which independently influenced survival after resection of recurrent cancer ($P < 0{\cdot}001$). The 5-year survival rates were 38 per cent in the localized type ($n = 27$), 10 per cent in the sacral invasive type ($n = 16$) and zero in the lateral invasive type ($n = 17$).

Conclusion: Resection for locally recurrent rectal cancer is potentially curative in patients with localized or sacral invasive patterns of recurrence. Alternatives should be explored in patients with recurrence involving the lateral pelvic wall.

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Introduction

Local recurrence of rectal cancer in the pelvis is a common problem after potentially curative resection, with an incidence varying between 5 and 35 per cent[1–4]. Although there have been distinct improvements in therapeutic strategies for recurrent liver metastases of colorectal cancer, such as hepatic resection and hepatic infusional chemotherapy[5–7], treatment for local recurrence remains a difficult clinical problem. Patients who have no treatment for local recurrence not only have a short life expectancy, but often experience disabling and sometimes intolerable pain. Radiotherapy is temporarily effective in improving quality of life but it is not curative and may have considerable side-effects. Only radical resection of the recurrent tumour offers an improvement in prognosis. However, this option should be considered only in a carefully selected population, as procedures that include total pelvic exenteration or distal sacrectomy are associated with considerable morbidity and mortality rates. Half of the local recurrences occur without disseminated disease[1–3] but the 5-year survival rate after curative reoperation is less than 30 per cent[3,8–13]. Many factors, such as the characteristics of both the primary and recurrent tumours and the extent of resection for recurrent tumour, may contribute to an unfavourable prognosis. The authors reported previously that the pattern of pelvic recurrence (localized, sacral or lateral) influenced prognosis after resection and was useful in patient selection[14]. In this study, various prognostic factors in surgery for locally recurrent rectal cancer were studied retrospectively by multivariate analysis.

Patients and methods

Between January 1983 and December 1999, 83 consecutive patients with local recurrence of rectal cancer were treated at the First Department of Surgery, Kagoshima University School of Medicine. In these patients, radical resection with wide mesenteric resection and high ligation of the inferior mesenteric artery had been performed with curative intent for primary rectal carcinomas, which were located in the upper rectum in 34 patients and in the lower rectum in 49.

Table 1 Patterns of pelvic invasion of local recurrence of rectal cancer

Localized type	Recurrent tumour is localized to adjacent pelvic organs or connective tissue
Sacral invasive type	Recurrent tumour invades the lower sacrum (S3, S4, S5), coccyx or periosteum
Lateral invasive type	Recurrent tumour invades the sciatic nerve, greater sciatic foramen, lateral pelvic wall or upper sacrum (S1, S2)

The primary surgical procedure was a sphincter-saving procedure (SSP) in 39 patients and abdominoperineal resection (APR) in 44 patients. Iliopelvic lymphadenectomy had been performed in 28 patients. Although most patients had undergone postoperative chemotherapy with 5-fluorouracil administered either intravenously or orally, adjuvant radiotherapy had not been used.

Local recurrence occurred at a median of 609 (interquartile range 342–951) days after the initial operation. Distant metastases were excluded by chest radiography, abdominal ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), available since 1990, and in some cases bone scintigraphy. Primary tumour stage was confirmed histopathologically and analysed according to Dukes' classification. The extent of the recurrent tumour was defined by CT, MRI, abdominal ultrasonography and endorectal ultrasonography (EUS), and confirmed histopathologically in patients who subsequently underwent resection of the locally recurrent tumour. Patients were classified according to the pattern of pelvic invasion of the recurrent tumour (*Table 1*). Each pattern was determined by preoperative imaging and confirmed histopathologically. Serum carcinoembryonic antigen (CEA) concentration (normal range below 5 ng/ml) was measured in all patients before resection of recurrent rectal cancer.

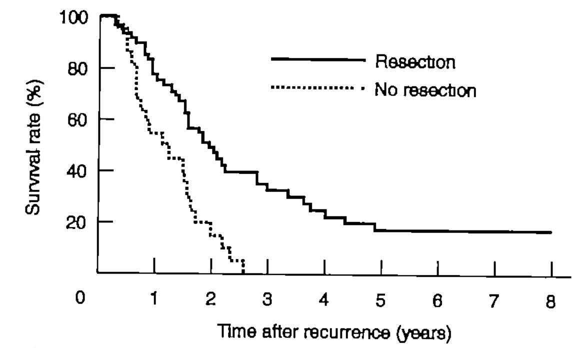
Treatment of recurrence

Sixty patients had a potentially curative wide resection of the local recurrence. This included a further abdominal resection in two patients, APR in six patients, APR with sacral resection in seven patients, subtotal pelvic exenteration in 15 patients, total pelvic exenteration in 14 patients, and total pelvic exenteration with sacral resection in 16 patients. Total pelvic exenteration was accompanied by urinary reconstruction using an ileal conduit. The extent of sacral resection was limited to the distal sacrum below S2. Adjuvant radiotherapy or chemotherapy was not used, although four patients underwent radiotherapy for palliation of intolerable pain, which was caused by re-recurrence in the pelvis after resection for local recurrence. The clinical and pathological characteristics of these patients are summarized in *Table 2*. Surgical resection was not attempted in 23 patients owing to irresectable local disease, as judged by preoperative imaging and intraoperative biopsy, or poor general health. These patients underwent conservative treatment including radiotherapy, iliac arterial infusional chemotherapy or diverting colostomy.

Table 2 Clinical and pathological characteristics of patients who underwent resection of locally recurrent rectal cancer

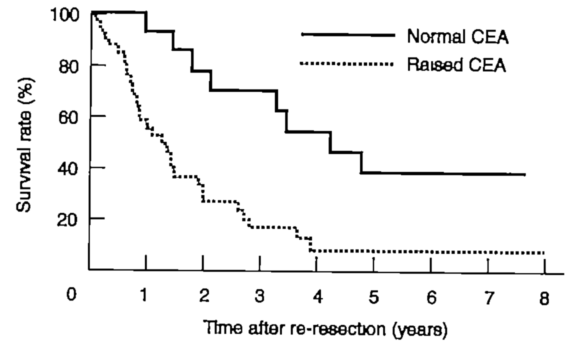
	No. of patients
Age (years)	
< 60	29
⩾ 60	31
Sex	
Male	38
Female	22
Interval to recurrence (days)	
< 600	30
⩾ 600	30
Recurrent disease	
Symptoms	
Severe	35
Mild or absent	25
CEA	
Normal	18
Raised	42
Histology*	
Well	28
Moderately or poorly	32
Pelvic invasive pattern	
Localized type	27
Sacral invasive type	16
Lateral invasive type	17
Primary disease	
Location	
Upper rectum	24
Lower rectum	36
Dukes' stage	
A	7
B	16
C	37
Histology*	
Well	40
Moderately or poorly	20
Venous invasion	
Yes	24
No	36
Lymphatic invasion	
Yes	47
No	13
Surgical procedure	
SSP	32
APR	28

*Differentiation of adenocarcinoma. CEA, carcinoembryonic antigen; SSP, sphincter-saving procedure; APR, abdominoperineal resection



No. at risk									
Resection	60	43	21	14	10	7	7	6	2
No resection	23	11	4	0					

Fig. 1 Survival after recurrence in patients who underwent resection ($n = 60$) or conservative treatment ($n = 23$) for locally recurrent rectal cancer. $P < 0{\cdot}001$ (log rank test)

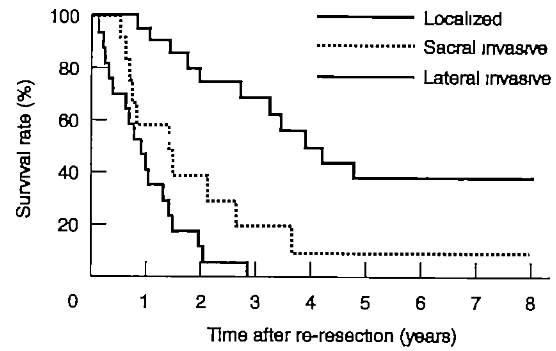


No. at risk									
Normal CEA	18	15	10	9	7	5	5	4	0
Raised CEA	42	22	8	5	2	2	2	2	2

Fig. 2 Survival after re-resection in patients with normal ($n = 18$) or raised ($n = 42$) serum levels of carcinoembryonic antigen (CEA). $P < 0{\cdot}001$ (log rank test)

Statistical analysis

Survival time was calculated from the start date of treatment for local recurrence of rectal cancer until the last follow-up attendance, or death. The cumulative survival rate following treatment was calculated using the Kaplan–Meier method. Univariate and multivariate analyses were performed with the Cox proportional hazards model to identify factors that independently influenced survival. Maximum likelihood parameter estimates and likelihood ratio statistics in the Cox proportional hazards models were obtained with the use of a statistical package (EPICURE®; HiroSoft International, Seattle, Washington, USA). All *P* values presented are two sided, and the level of significance was defined as $P < 0{\cdot}05$.



No at risk									
Localized	27	24	13	12	8	6	6	5	1
Sacral invasive	16	6	4	2	1	1	1	1	1
Lateral invasive	17	7	1	0					

Fig. 3 Survival after re-resection according to pelvic invasive pattern of local recurrence. $P < 0{\cdot}001$ (log rank test)

Results

The pattern of pelvic invasion in the 60 patients who underwent resection for locally recurrent tumour was confirmed histopathologically as localized type in 27 patients, sacral invasive type in 16 patients and lateral invasive type in 17 patients. In the 23 patients who underwent conservative treatment, the tumour was diagnosed as sacral invasive type in two patients and lateral invasive type in the remaining 21 patients. Two patients died in hospital after resection of recurrent cancer, resulting in an operative mortality rate of 3 per cent. The 5-year survival rate among patients who had the recurrent tumour resected was 18 per cent, which was significantly higher than that of patients who were treated non-surgically ($P < 0{\cdot}001$) (*Fig. 1*). Seven patients have survived longer than 5 years after re-resection without recurrent disease. One patient underwent a pulmonary resection for lung metastasis approximately 3 years after resection for local recurrence.

Prognostic factors after resection

Univariate analysis of survival rates after resection of locally recurrent tumour was performed according to clinical, histopathological and surgical factors. Eighteen patients with serum CEA levels within normal limits had a significantly higher rate of survival than the 42 patients with raised serum CEA levels (5-year survival rate 39 *versus* 8 per cent; $P < 0{\cdot}001$) (*Fig. 2*). A significant difference in survival after re-resection was seen according to the pattern of pelvic invasion of locally recurrent cancer ($P < 0{\cdot}001$).

Table 3 Univariate and multivariate analyses of prognostic factors in patients who underwent resection of locally recurrent rectal cancer

	Univariate analysis	Multivariate analysis†	
	P	Hazard ratio	*P*
Age (< 60 *versus* ≥ 60 years)	0·35	—	
Sex (male *versus* female)	0·06	—	
Interval to recurrence (< 600 *versus* ≥ 600 days)	0·22	—	
Recurrent disease			
Symptoms (severe *versus* mild or absent)	0·40	—	
CEA (normal *versus* raised)	< 0·001	1·62 (0·61–4·31)	0·33
Histology* (well *versus* moderately or poorly)	0·08	—	
Pelvic invasive pattern	< 0·001		< 0·001
Localized *versus* sacral invasive type		2·70 (1·01–7·26)	
Localized *versus* lateral invasive type		6·73 (2·50–18·14)	
Sacral resection (yes *versus* no)	0·82	—	

Values in parentheses are 95 per cent confidence intervals. *Differentiation of adenocarcinoma. CEA, carcinoembryonic antigen. †Cox proportional hazards model

The 5-year survival rate was 38 per cent in patients with the localized type, 10 per cent in those with the sacral invasive type and zero in patients with the lateral invasive type (*Fig. 3*). Age (less than 60 years or 60 years or more), sex and time to recurrence (less than 600 days or 600 days or more), symptoms, histology and sacral resection at recurrence, as well as location, Dukes' stage, initial histology, venous invasion, lymphatic invasion and surgical procedure (SSP *versus* APR) of primary disease were not significantly related to survival after re-resection.

Multivariate analysis revealed that only the pelvic invasive pattern independently influenced survival after resection for locally recurrent rectal cancer ($P < 0·001$). Patients with the localized type of recurrence had a significantly better prognosis, but recurrences of sacral invasive types (hazard ratio 2·70) and lateral invasive types (hazard ratio 6·73) were found to be unfavourable prognostic factors (*Table 3*).

Discussion

The pelvis is a predominant site of recurrent disease after potentially curative resection for rectal cancer. Whether alone or in combination with other sites, the pelvis is often the earliest site of recurrent disease[2]. Patients with local recurrence of rectal cancer have an unfavourable prognosis if untreated, and survive for a shorter time than those with distant spread[3]. It has been shown, however, that approximately half of the patients who develop local recurrence had cancers confined to the pelvis, with no distant metastases at a second-look operation or autopsy[15,16]. It is this population of patients, with only locally recurrent cancers, in whom an aggressive approach should be attempted, including extensive surgery. The present series excluded patients with distant metastases and adopted an extensive resection approach for recurrent cancer, to obtain surgically free margins if technically possible, without additional radiotherapy.

An important obstacle to treatment is the problem of detecting local recurrence early enough to achieve a curative reoperation. A combination of history, physical examination, CEA measurement, endoscopy, and imaging by abdominal ultrasonography, EUS, CT and MRI may help to detect recurrent tumour early, although early detection is difficult even with close surveillance. Symptoms frequently precede the biochemical or imaging evidence of recurrence. Moreover, false-negative results make serial estimations of CEA level unreliable[17] and insufficiently early detection of small recurrent tumours by CT or MRI has been reported previously[18,19]. In the present series, locally recurrent tumours with the localized type of invasion pattern were diagnosed earliest. CT-guided fine-needle biopsy after APR and EUS after SSP are useful for early detection of locally recurrent tumour[20], so these diagnostic methods were used for tumours of the localized type. Recent studies have indicated that positron emission tomography may be more sensitive than CT or MRI for the detection of locally recurrent rectal cancer and may improve its clinical management[21,22].

In patients with local recurrence that is not amenable to resection owing to extensive invasion or fixation to an irresectable structure, such as the lateral invasive type, isolated pelvic perfusion chemotherapy[23], or radiotherapy alone or in combination with resection, may shrink the recurrence and facilitate resection. Radiotherapy alone may achieve palliation in 60–80 per cent of patients. However, this effect lasts only 3–6 months in the majority of cases, and most patients do not survive more than 2 or 3 years after recurrence[24,25]. In the present series, the survival of patients treated by radiation was not different from that of those who received no radiation. Three of the present patients received iliac arterial infusional chemotherapy with cisplatin. A complete response was observed in one patient but there were no long-term survivors. Preoperative irradiation for pelvic recurrent tumour may be related directly to postoperative mortality[26]. Furthermore, in radiation therapy the peripheral nerve is known to be the principal dose-limiting structure and the ureter is also dose sensitive. In patients who received intraoperative electron beam radiation, 33 per cent suffered peripheral neuropathy and 44 per cent developed stenosis of the ureter[13,27]. Several reports outlining favourable results in the use of chemoradiation for locally recurrent rectal cancer have been published recently[28,29], although these conservative treatments are not considered to be well tolerated or to increase survival.

Resection of local recurrence probably offers the best chance for improved local control and prognosis, but may need to be radical, carrying a significant risk of morbidity and death. In most recent studies, however, the perioperative mortality rate of resection for local recurrence has been reported to be well under 5 per cent[8,11,12,30,31]. Although more extensive procedures such as abdominal sacral resection and inferior pelvectomy have been performed, Wenebo *et al.*[10,32] and Maetani *et al.*[9] reported a relatively low mortality rate of 8 and 6 per cent respectively. In the present series, most patients had undergone posterior or total pelvic exenteration including distal sacrectomy, with a mortality rate of 3 per cent, which is comparable to these results. These favourable results arise from the fact that such radical salvage procedures were undertaken only in specialized centres where a multidisciplinary team familiar with this type of complex problem was available. It is also important that a complete preoperative evaluation be carried out to define the extent of disease and avoid offering inappropriately radical procedures.

In cases of locally recurrent rectal cancer, few reports deal with factors that potentially influence survival after re-resection. Most authors agree that survival after re-resection depends mainly on complete resection with negative pathological resection margins[8–11,13,30–32]. Therefore, identifying factors that can evaluate individual patient suitability for this approach is advantageous and may be used to predict outcome after re-resection. Several factors, such as type of initial operation (SSP or APR), the presence of severe symptoms, diameter of recurrent tumour, tumour growth rate and CEA level before re-resection, have been considered to be significant prognostic indicators after re-resection, although a consensus has not been achieved[8,10–12,33,34]. In the present series, classification of the pattern of pelvic invasion by recurrent tumour was the only factor that independently influenced the 5-year survival rate after re-resection. However, whether the pelvic invasive pattern can be diagnosed accurately before operation must be addressed. Imaging procedures such as CT and MRI are valuable in diagnosing the extent of recurrent tumour. MRI is especially useful in displaying the proximal extent of sacral involvement[18,35]. Although in this study the classification of pelvic invasion was strictly evaluated by findings at operation and postoperative histological results, it may be possible to define the extent of disease before operation.

In conclusion, surgical resection for local recurrence of rectal cancer seems to be acceptable as a potentially curative treatment. The type of pelvic invasion is closely associated with survival after re-resection.

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Criteria for extramural perineural invasion as a prognostic factor in rectal cancer

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Background: An abundant extramural autonomic nerve network is an anatomical feature of the rectum. Extramural perineural invasion (PNI) may influence the prognosis after resection of rectal cancer, however, few assessment criteria exist.

Methods: PNI was investigated in 364 patients who underwent curative surgery for rectal cancer penetrating the muscular layer. A grading system was established based on the 'intensity' (number of PNI foci in a 20-power field) and 'depth' (distance from the muscularis propria) of PNI. PNI-0 was defined as without PNI, PNI-1 as 'intensity' of less than five foci and 'depth' less than 10 mm, and PNI-2 as five or more foci or 10 mm or greater 'depth' of invasion.

Results: PNI was observed in 52 patients (14 per cent) and strongly correlated with pathological tumour node metastasis (pTNM) stage. Five-year survival was related to PNI grade (74 per cent in PNI-0, 50 per cent in PNI-1 and 22 per cent in PNI-2). The rate of local recurrence was also related to PNI stage: 43 per cent in PNI-2 and 9 per cent in both PNI-0 and PNI-1. Multivariate analyses showed that graded PNI was associated both with local recurrence and long-term survival, independent of tumour depth (pTNM T) and nodal involvement (pTNM N).

Conclusion: The PNI grading system may be useful in prognosis and allow case selection for intensive postoperative adjuvant therapy.

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Introduction

Tumour penetration depth and lymph node metastasis have long been regarded as the standard prognostic determinants for patients with colorectal cancer[1-4]. These factors are used widely for prognostic classification, such as Dukes' staging[1] or tumour node metastasis (TNM) classification[4]. However, some investigators report that these are insufficient and emphasize the need to develop variables related to tumour growth characteristics[5-7].

A complex network of autonomic nerves envelops the rectum. Since Seefeld and Bargen's report[8], many investigators have noted that perineural invasion (PNI) by tumour has significance as an indicator of survival[9-17] and local recurrence[8,12,18,19]. However, there has been little work on development of an objective grading system of PNI that might be useful in selecting patients for postoperative adjuvant therapy. In this paper, the prognostic value of extramural PNI was evaluated and its role among assessment criteria in patients undergoing rectal cancer surgery was determined.

Patients and methods

Patients

Five hundred and sixty-one patients underwent resection of a primary rectal cancer, histologically confirmed as penetrating the muscularis propria, at the First Department of Surgery of the National Defense Medical College Hospital between 1981 and 1995. Some 197 patients who had distant metastases or histologically confirmed involvement of the surgical resection margin[20] were excluded and the 364 patients who were operated on with curative intent were the subject of this study. Preoperative adjuvant therapies were not used for patients with rectal cancer during this period. In the study group there were 222 men and 142 women with a mean age of 60·6 (range 31-86) years. The location of the lower edge of the tumour was above the peritoneal reflection in 165 patients and below it in 199 patients. Sphincter-saving surgery was performed in 216 patients, abdominoperineal resection in 131 patients, total pelvic exenteration in ten patients and Hartmann's procedure in seven patients. The mean follow-up of the 214 survivors was 92·0 months. During the study, nerve-preserving surgery was not carried out for patients with rectal cancer penetrating the muscularis propria, and the dissection was performed along the outer layer of the autonomic nervous system.

Histological examination

Histological features of known prognostic importance, i.e. tumour penetration depth, number of lymph nodes involved and the degree of vascular invasion based on the Japanese Classification of Colorectal Carcinoma[20], had been recorded previously in the pathological reports. Regarding the degree of vascular invasion, lymphatic and venous invasion was each divided into two grades: none or minimal invasion, and moderate and severe invasion. The pathological stage of tumours was defined according to the pTNM classification system (5th edition, 1997)[4]. The median count of lymph nodes examined in each case was 23 in this cohort.

Extramural PNI was judged by one of the authors (H.U.) who was blinded to patient outcome. All pathological specimens, which were routinely processed and stained with haematoxylin and eosin, were reviewed. A median of four slides per case included the part of extramural cancer penetration. A positive judgement of PNI was made when cancer cells were found to exist inside the perineurium (*Fig. 1*). After meticulous investigation to choose the field in which PNI was most intensive, the number of PNI foci was counted with a microscopic field of × 20 ('intensity' of PNI) (*Fig. 2*). The distance between the outermost focus of PNI and the outer margin of the muscularis propria was also measured as the 'depth' of PNI (*Fig. 2*). When the outer aspect of the muscular layer could not be estimated because of its destruction by tumour, an estimate was made by drawing a straight line between both break points of the outer aspect of the muscular layer. Furthermore, when PNI represented the invasive front of the tumour, the distance between the isolated focus of PNI at the most invasive frontal position and a neighbouring cancer focus of other spread type, such as vessel invasion, was measured.

Prognosis

With regard to local recurrence, there are differences in mechanism between anastomotic recurrence and pelvic recurrence other than at the anastomosis. In this study, recurrence was investigated with special reference to pelvic recurrence, excluding anastomotic recurrence that occurred as a result of an insufficient distal margin of tumour or cancer implantation at an anastomotic site. The influence of PNI on survival and local recurrence was analysed by univariate and multivariate analysis (stepwise regression analysis) based on Cox's proportional hazards model or by logistic analysis using the SPSS® programs (Medical Pack 6.1 J for Macintosh; SPSS, Chicago, Illinois, USA). Survival was estimated using the Kaplan–Meier method and was tested for statistical differences between various subgroups by means of the log rank test.

Results

PNI was observed in 52 patients (14 per cent). The tumour location and maximum diameter did not correlate with PNI. On the other hand, the incidence of PNI was significantly related to tumour differentiation, the degree of lymphatic and venous invasion, pTNM T and pTNM N (*Table 1*). The incidence of PNI increased with progression

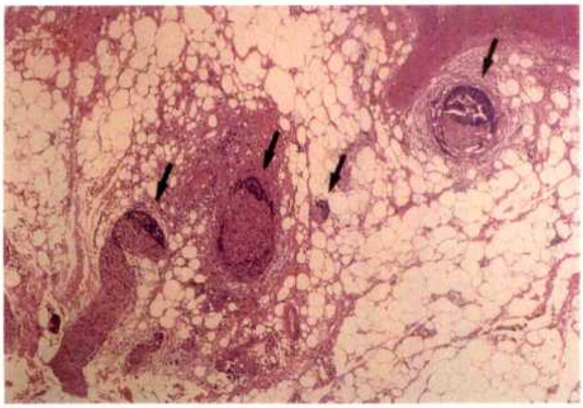


Fig. 1 Histological finding of extramural perineural invasion (arrows) (haemotoxylin-eosin counterstain, original magnification × 13)

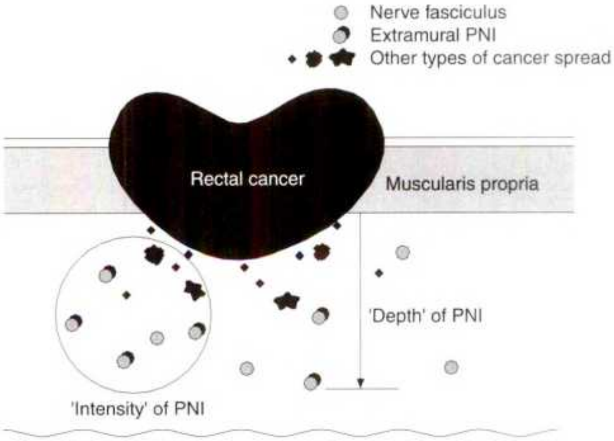


Fig. 2 Estimation of extramural perineural invasion (PNI)

of the pTNM stage; 4 per cent in stage II and 24 per cent in stage III. Among patients with PNI, the isolated PNI focus was separated from other types of spread by more than 1000 μm (maximum 6000 μm) in 20 patients (38 per cent).

Overall survival of patients with PNI was worse than that of patients without PNI (5-year survival rate 35 and 74 per cent respectively; $P < 0·001$) (*Table 1*).

Table 1 Extramural perineural invasion and other clinicopathological characteristics of patients undergoing curative resection of rectal cancer

	No PNI	PNI	*P*
Differentiation			
Well	94	7 (7)	0·013*
Moderate	206	42 (17)	
Other	12	3 (20)	
Lymphatic invasion			
None, minimal	205	14 (6)	< 0·001
Moderate, severe	107	38 (26)	
Venous invasion			
None, minimal	240	22 (8)	< 0·001
Moderate, severe	72	30 (29)	
pTNM T			
pT_3	292	44 (13)	0·043
pT_4	20	8 (29)	
pTNM N			
pN_0	163	6 (4)	< 0·001†
pN_1	100	21 (17)	0·009‡
pN_2	49	25 (34)	
TNM stage			
II	163	6 (4)	< 0·001
III	149	46 (24)	
5-year survival (%)	74	35	< 0·001

Values in parentheses are percentages. PNI, perineural invasion; pTNM, pathological tumour node metastasis. **Versus* moderate and others; †*versus* pN_1; ‡*versus* pN_2 (χ^2 test)

Grading of perineural invasion

Seventeen patients had five or more PNI foci per 20-power field. The odds ratio of local recurrence was 3·1 (95 per cent confidence interval (c.i.) 1·3–7·6) in patients with a PNI 'intensity' of less than five and 7·4 (2·6–21·0) in patients with a PNI 'intensity' of five or more, compared with patients without PNI (*Table 2*).

Regarding the 'depth' of PNI, a deeply located PNI (10 mm or more) was observed in 28 patients. There was no difference in local recurrence rate between patients without PNI and patients with a 'depth' of less than 10 mm (9 and 12 per cent respectively); however, patients with a more deeply located PNI had a local recurrence rate of 43 per cent (*Table 2*).

Univariate analysis of survival using Cox's proportional hazards model showed that the hazard ratio increased with the PNI 'intensity' and 'depth' (*Table 2*). The three-point grading of PNI was thus established: PNI-0, no PNI; PNI-1, 'intensity' less than five foci and/or 'depth' less than 10 mm; and PNI-2, 'intensity' five or more foci and/or 'depth' of invasion 10 mm or greater.

Prognostic value of the perineural invasion grading system

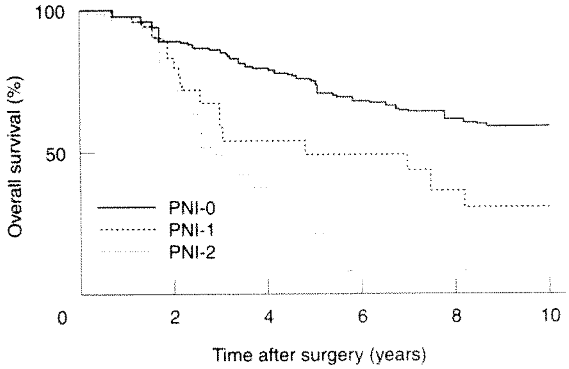
Based on the PNI grading system, there were 22 patients with PNI-1 and 30 with PNI-2. Survival worsened with increasing PNI grade (*Fig. 3*). Multivariate analysis showed that PNI grading was of independent prognostic significance, as was the pTNM N and pTNM T grading system (*Table 3*).

Patients with PNI-1 had a local recurrence rate of 9 per cent, as did those with PNI-0, while 43 per cent of patients with PNI-2 developed local recurrence (*Table 4*). Stepwise

Table 2 Impact of extramural perineural invasion with regard to 'intensity' and 'depth' on local recurrence and postoperative survival of patients undergoing curative resection of rectal cancer

	No. of patients	Local recurrence		Survival	
		Incidence (%)	Odds ratio*	5-year (%)	Hazard ratio†
'Intensity' of PNI					
No PNI	312	9	1	74	1
1–4 per 20-power field	35	23	3·1 (1·3–7·6)	44	2·6 (1·7–4·0)
≥ 5 per 20-power field	17	41	7·4 (2·6–21·0)	14	4·6 (2·7–7·9)
'Depth' of PNI‡					
No PNI	312	9	1	74	1
< 10 mm	24	12	1·5 (0·4–5·4)	46	2·3 (1·4–3·9)
≥ 10 mm	28	43	7·9 (3·4–18·5)	24	4·1 (2·6–6·5)

Values in parentheses are 95 per cent confidence intervals. *Logistic analysis; †univariate analysis using Cox's proportional hazard model. ‡Length between the outermost focus of perineural invasion (PNI) and the outer margin of muscularis propria



No. at risk						
PNI-0	312	277	214	140	87	57
PNI-1	22	16	12	9	6	2
PNI-2	30	23	9	2	2	1

Fig. 3 Survival of patients who underwent curative surgery for rectal cancer penetrating the muscularis propria, according to grade of perineural invasion (PNI). $P = 0·007$, PNI-0 *versus* PNI-1; $P = 0·05$, PNI-1 *versus* PNI-2; $P < 0·0001$, PNI-0 *versus* PNI-2 (log rank test)

regression analysis of PNI, pTNM N, and pTNM T showed that the risk of local recurrence increased with PNI-2 (odds ratio 5·4 (95 per cent c.i. 2·3–12·8)) and pN$_2$ (odds ratio 3·4 (1·3–8·8)); pTNM T was not an independent determinant of local recurrence. With respect to the patients with local recurrence, one of 15 PNI-positive patients had recurrence localized in the pelvic region compared with 11 of 27 PNI-negative patients ($P < 0·05$, Fisher's exact test).

Prognostic analyses were performed among three patient groups: (1) patients with neither nodal involvement nor PNI, (2) patients with either pN$_1$ or PNI-1 and (3) patients with either pN$_2$ or PNI-2. There was no significant difference in risk of local recurrence between patients without nodal involvement and PNI and patients with pN$_1$ and/or PNI-1. The risk of local recurrence was increased 6·7 times in patients with pN$_2$ and/or PNI-2 (odds ratio 6·7 (95 per cent c.i. 2·8–15·6)) (*Table 5*). Among patients with local recurrence, the proportion of patients whose recurrence was localized intrapelvically was 63 per cent (five of eight) in patients with neither nodal involvement nor PNI, but 27 (three of 11) and 17 (four of 23) per cent in patients with pN$_1$ and/or PNI-1 and pN$_2$ and/or PNI-2 respectively. The distribution of the survival curves based on the classification combining pTNM N and PNI grading was significantly different between the groups (*Fig. 4*).

Table 3 Survival analysis using Cox's proportional hazard model

	No. of patients	5-year survival (%)	Hazard ratio Univariate analysis	Multivariate analysis*
PNI				
PNI-0	312	74	1	1
PNI-1	22	50	2·1 (1·2–3·7)	1·5 (0·8–2·6)
PNI-2	30	22	4·2 (2·7–6·5)	2·6 (1·6–4·2)
pTNM N				
pN$_0$	169	82	1	1
pN$_1$	121	64	1·9 (1·3–2·8)	1·8 (1·2–2·7)
pN$_2$	74	42	3·8 (2·5–5·7)	2·9 (1·9–4·5)
pTNM T				
pT$_3$	336	68	1	1
pT$_4$	28	48	2·4 (1·4–4·0)	2·3 (1·4–3·9)

Values in parentheses are 95 per cent confidence intervals.
*Stepwise regression analysis. Variables analysed by multivariate analysis: (1) perineural invasion (PNI) (PNI-0 = 0, PNI-1 = 1, PNI-2 = 2); (2) pathological tumour node metastasis (pTNM) N (pN$_0$ = 0, pN$_1$ = 1, pN$_2$ = 2); and (3) pTNM T (pT$_3$ = 0, pT$_4$ = 1)

Table 4 Logistic analysis for the risk of local recurrence after curative surgery

	No. of patients	Local recurrence (%)	Odds ratio Univariate analysis	Multivariate analysis*
PNI				
PNI-0	312	9	1	1
PNI-1	22	9	1·1 (0·2–4·8)	0·7 (0·2–3·3)
PNI-2	30	43	8·1 (3·5–18·4)	5·4 (2·3–12·8)
pTNM N				
pN$_0$	169	5	1	1
pN$_1$	121	14	2·9 (1·3–6·8)	2·3 (0·9–5·4)
pN$_2$	74	22	4·9 (2·1–11·7)	3·4 (1·3–8·8)
pTNM T				
pT$_3$	336	11	1	–
pT$_4$	28	21	2·3 (0·9–6·0)	–

Values in parentheses are 95 per cent confidence intervals.
*Stepwise regression analysis. Variables analysed by multivariate analysis: (1) perineural invasion (PNI) (PNI-0 = 0, PNI-1 = 1, PNI-2 = 2); (2) pathological tumour node metastasis (pTNM) N (pN$_0$ = 0, pN$_1$ = 1, pN$_2$ = 2); and (3) pTNM T (pT$_3$ = 0, pT$_4$ = 1)

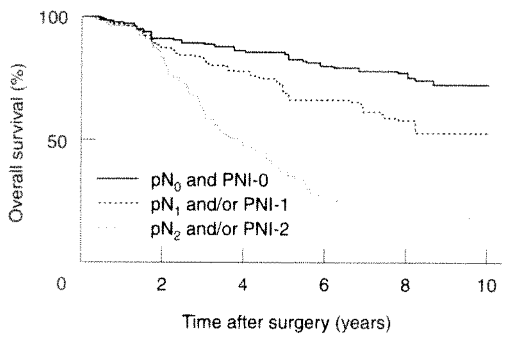
Discussion

The potential value of nerve-preserving surgery for rectal cancer has been highlighted in Western countries[19,21–23] and in Japan[24–27]. However, extramural PNI must have a direct impact on the prognostic outcome after this procedure. Previous research has shown that microscopic PNI foci separate from the primary tumour have a significant influence on outcome[28], although cancer inva-

Table 5 Risk of local recurrence and death based on perineural invasion and node involvement

	No. of patients	Local recurrence		Survival	
		Incidence (%)	Odds ratio*	5-year (%)	Hazard ratio†
pN_0 and PNI-0	163	5	1	83	1
pN_1 and/or PNI-1	111	10	2·1 (0·8–5·5)	70	1·6 (1·1–2·5)
pN_2 and/or PNI-2	90	26	6·7 (2·8–15·6)	38	4·4 (3·0–6·6)

Values in parentheses are 95 per cent confidence intervals. *Logistic analysis; †Cox's proportional hazard model. PNI, perineural invasion; pN, nodal status in pathological tumour node metastasis classification



No. at risk						
pN_0 and PNI-0	163	145	120	83	56	38
pN_1 and/or PNI-1	111	98	78	53	30	22
pN_2 and/or PNI-2	90	73	37	15	9	3

Fig. 4 Survival of patients who underwent curative surgery for rectal cancer, according to pathological tumour node metastasis pN category and grade of extramural perineural invasion (PNI). P = 0·01, pN_0 and PNI-0 *versus* pN_1 and/or PNI-1; P < 0·0001, pN_2 and/or PNI-2 *versus* pN_0 and PNI-0, and pN_1 and/or PNI-1(log rank test)

sion restricted to the Meissner or Auerbach nerve plexus was not important as a prognostic determinant[29]. The perineural space is not a part of the lymphatic system[30,31]. However, 'isolated' PNI foci 1000 μm or more away from other forms of cancer invasion were observed in 38 per cent of patients with PNI in the present study. Thus the perineural space should be recognized as a potential route for the spread of rectal cancer[8,32].

In this series, patients in the PNI-2 group showed a high incidence of local recurrence, although they underwent an extended resection to include the nerve plexus. Based on the examination of the pelvic plexus, which was serially excised from the resected rectum and sectioned totally, nerve plexus involvement was discovered in 10–15 per cent of patients who underwent extended resection of the rectum with the associated nervous system[33–35]. The depressing survival outcome of patients with such autonomic nerve plexus involvement has been reported previously[35]. Although the pelvic nerve plexus could not be clearly distinguished from the particularly rich plexus of autonomic nerves in the mesorectum (rectal branch of the nerve) in this retrospective study, some PNI with a 'depth' of 10 mm or more might be PNI in the pelvic plexus. The distance between the pelvic plexus and the rectal muscularis propria has been reported to be 8·3 ± 3·5 mm in fixed specimens[36]. On the other hand, a significant link between PNI and local recurrence after total mesorectal excision with nerve preservation has also been reported[19]. These results indicate that PNI represents an unfavourable prognostic finding irrespective of the degree of dissection. In such patients, surgical resection alone is insufficient to cure the disease.

A prognostic classification based on PNI and TNM N creates a well distributed classification that distinguishes patients who have rectal cancer penetrating the muscular layer with and without a risk of local recurrence. Based on this division, the subset with the highest risk of local recurrence can be determined, i.e. patients with pN_2 and/or PNI-2. Bentzen *et al.*[37] reported that patients with high-risk factors for local recurrence, including PNI, had a statistically significant benefit from postoperative radiotherapy, but this did not extend to overall survival. Further, Enker *et al.*[19] reported that the risk factors for local failure after total mesorectal excision were N_2 disease and PNI. In patients with these features, systemic metastases far outweighed local failure. These reports appear to be compatible with the present finding that more than 80 per cent of patients with pTNM N_2 and/or PNI-2 who developed local recurrence also had a systemic recurrence.

Some prognostic classifications based on variables related to the manner of invasion, besides nodal stage and penetration depth, have been reported[5,6]. They are not used widely, because of the difficulty of objective judgement. PNI grading, as shown in this study, can be estimated easily. Although the number of patients with PNI is small, it could possibly be a criterion for case selection for intensive adjuvant therapy of patients with nodal involvement, together with the number of nodes involved. Further multi-institutional studies based on a large collective database will confirm the validity of this PNI grading system.

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Original article

Randomized study of coagulation and fibrinolysis during and after gasless and conventional laparoscopic cholecystectomy

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Background: Carbon dioxide pneumoperitoneum may be an important pathophysiological factor stimulating the coagulation system during conventional laparoscopic cholecystectomy. The aim of this study was to test the hypothesis that gasless laparoscopy produces smaller changes in the coagulation and fibrinolytic system than carbon dioxide pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

Methods: Fifty patients were allocated randomly to conventional ($n = 26$) or gasless ($n = 24$) laparoscopic cholecystectomy. Blood samples were obtained on admission, after induction of anaesthesia, after insufflation or traction, 30 min after introduction of the laparoscope, 10 min after exsufflation of carbon dioxide or traction, 4 h after extubation and 24 h after operation.

Results: The two groups were comparable with respect to age, sex, body mass index and duration of operation. Plasma levels of prothrombin fragment 1 and 2 (F1 + 2), soluble fibrin and D-dimer did not differ between the two groups. F1 + 2 levels varied significantly in both groups during and after operation ($P < 0.001$). Soluble fibrin and D-dimer levels did not change during operation in either group, but after operation the levels increased significantly in both groups ($P < 0.001$).

Conclusion: Carbon dioxide pneumoperitoneum does not enhance the activation of coagulation and fibrinolysis associated with laparoscopic cholecystectomy. The coagulation and fibrinolytic systems are activated during and after gasless as well as conventional laparoscopic cholecystectomy.

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Introduction

Conventional laparoscopic cholecystectomy (CLC) with insufflation of carbon dioxide induces activation of the coagulation and fibrinolytic systems[1,2]. This activation may be monitored by measurement of certain markers of coagulation and fibrinolysis in plasma. Although CLC is regarded as a minimally invasive procedure avoiding much of the tissue injury associated with traditional laparotomy, the perioperative changes in plasma levels of these coagulation markers do not seem substantially different from those found after open upper abdominal surgery[3]. The clinical consequences of these changes, with regard to thromboembolic complications, are not known, nor are the pathophysiological mechanisms triggering the coagulation system. A comparative study has shown a lower incidence of deep vein thrombosis (DVT) after CLC than after open cholecystectomy[4], but reported incidences vary considerably between studies (0·05–55 per cent)[5–7]. It remains to be determined whether the risk of postoperative DVT is associated with the leg vein stasis induced by the carbon dioxide pneumoperitoneum and the reverse Trendelenburg position of the patient during CLC[8,9].

Recently, a number of mechanical elevators of the anterior abdominal wall have been developed to perform gasless laparoscopy in an attempt to profit from the minimally invasive approach without inducing the pathophysiological changes associated with CLC[10–12]. The aim of this study was to test the hypothesis that gasless laparoscopy leads to less activation of coagulation and fibrinolysis than carbon dioxide laparoscopy in patients allocated randomly to conventional or gasless laparoscopic cholecystectomy.

Patients and methods

Patients

Fifty consecutive patients with symptomatic cholecystolithiasis fulfilling the inclusion criteria were allocated randomly to laparoscopic cholecystectomy with either conventional carbon dioxide pneumoperitoneum (CLC) or a gasless technique (GLC). The allocation sequence was generated by random numbers. Patients were allocated randomly to the two groups by opening sealed envelopes on the day of operation. The intervention assignments were concealed from the patients and the ward nursing staff. Data were collected from 1 December 1998 to 1 October 1999.

All elective patients over the age of 18 years and with a body mass index (BMI) of 30 or less were informed and asked for written consent. Patients with acute pancreatitis, cholecystitis, cholangitis, blood diseases, rheumatic diseases, acute infectious diseases, renal or liver diseases were excluded from the study. The local ethics committee approved the study.

Operations

Three surgeons with experience of CLC and GLC performed all the operations. In one group (CLC), laparoscopic cholecystectomy was performed with conventional carbon dioxide pneumoperitoneum at a pressure of 12 mmHg, using two 10-mm and two 5-mm trocars. In the other group (GLC), two curved steel needles were inserted into the subcutaneous space and attached to a mechanical arm fixed to the operating table. A working chamber was produced by elevation of the mechanical retractor. A minilaparotomy (15 mm) was performed through the umbilicus. An unvalved 10-mm port was inserted and one 10-mm and two 5-mm unvalved ports were inserted under vision. After the working chamber had been created, cholecystectomy was performed using identical technique and instruments, a curved dissector and monopolar electrocautery. Cholangiography was not performed routinely. Once the cystic duct and artery had been clipped and divided, the gallbladder was detached from the liver bed and placed over the liver. The gallbladder was removed through the umbilical incision through a 20-mm port in the CLC group and through the 15-mm incision in the GLC group. Perioperative complications such as bleeding and perforation of the gallbladder were recorded. Gentamicin 240 mg was given to all patients 1 h before the procedure.

A diary was given to the patients at discharge to score pain and activity daily for 14 days. Nausea, dizziness, fatigue, pneumonia, wound complications and fever were recorded daily for 14 days.

Anaesthesia

To avoid interference with pulmonary or circulatory functions, patients were not premedicated. Local anaesthesia (bupivacaine 0·25 per cent) was injected before insertion of the ports and subdiaphragmatically after the gallbladder had been removed. Before induction of anaesthesia, sodium chloride 10 ml kg^{-1} was infused. Anaesthesia was induced with 2·5 mg midazolam and a bolus of propofol 2·5 mg kg^{-1} intravenously. The patient received fentanyl 5 µg kg^{-1} intravenously during the first hour of anaesthesia and a dose of 2·5 µg kg^{-1} in subsequent hours. Anaesthesia was maintained with propofol 12 mg kg^{-1} h^{-1}. Muscle relaxation was facilitated by cisatracurium 0·5 mg kg^{-1}. Patients were ventilated by means of a Servo 900 C-respirator (Siemens, Solna, Sweden) with a tidal volume of 7 ml kg^{-1} at a rate of 12 per min and inspired oxygen fraction of 0·30. Pulmonary peak pressure and pause pressure were measured to give an estimate of dynamic compliance. An antiemetic dose of ondansetron (4 mg intravenously) and ketoprofen (100 mg) was given 30 min before the expected time of extubation. Patients were given neostigmine–glycopyrronium (2·5 mg–0·4 mg) at the end of anaesthesia to prevent postanaesthetic relaxation. Finally, the patients were extubated.

After operation ketoprofen 100 mg twice daily and paracetamol 1 g four times daily were given as standard doses. Morphine injections were given and recorded when requested by the patient.

Blood collection and processing

Blood samples were obtained on admission (phase 1), after induction of anaesthesia (phase 2), after carbon dioxide insufflation or traction and introduction of the laparoscope (phase 3), 30 min after introduction of the laparoscope (phase 4), 10 min after exsufflation of carbon dioxide or traction (phase 5), 4 h after extubation (phase 6) and 24 h after operation (phase 7). A 21-G butterfly cannula was inserted, and Monovette® plastic vacuum tubes (Sarstedt, Numbrecht, Germany) containing 1 + 9 0·106 mol l^{-1} sodium citrate (final concentration 0·0106) and Stabilyte™ tubes with 1 + 9 0·5 mol l^{-1} citrate buffer (final concentration 0·05), pH 4·3, were filled. Brief stasis was applied to optimize venepuncture, but released before filling the tubes, and the first tube was discarded. Samples were cooled in melting crushed ice, while not handled. Blood was centrifuged within 30 min, at 4°C and 2000*g* for 20 min, and plasma was kept at −80°C until analysis.

Assays

The aim was to detect activation of coagulation and fibrinolysis *in vivo*; traditional assays are not well suited for this purpose, as they measure either plasma levels of clotting factors (which are zymogens normally present in great excess) or the velocity of *in vitro* clotting or fibrinolysis (i.e. processes taking place in the laboratory)[13]. Instead, use was made of commercially available immunoassays for products generated when coagulation or fibrinolysis is activated (*Fig. 1*). Prothrombin fragment 1 and 2 (F1 + 2) is a short-lived peptide released when prothrombin is converted to thrombin. Soluble fibrin is the soluble precursor of clots or thrombi, which form by aggregation of soluble fibrin and subsequent cross-linking. Lysis of such clots by plasmin releases cross-linked fibrin degradation products that may be identified by their neoantigen D-dimer. Key steps in coagulation and fibrinolysis (i.e. thrombin generation, fibrin generation and fibrinolysis) may thus be monitored by measurement of these markers (*Fig. 1*). F1 + 2 was measured by Enzygnost® F1 + 2 micro kit (Dade Behring, Marburg, Germany), a sandwich-type enzyme immunoassay (sEIA). Soluble fibrin was measured with the Enzymun-Test FM® (Boehringer Mannheim, Mannheim, Germany), a sEIA (measuring range 0·00–129·00 mg l^{-1}; intra-assay and interassay coefficient of variation (CV), 8·8 and 28·8 per cent respectively). D-Dimer was measured with the AGEN Dimertest® Gold EIA kit (AGEN Biomedical, Acacia Ridge, Queensland, Australia), a sEIA (assay range 0–2000 ng ml^{-1}; intra-assay and interassay CV, 11·3 and 27·9 per cent respectively).

Statistical analysis

The unpaired Mann–Whitney *U* test was used to compare data from the two study groups (CLC and GLC). Friedman's analysis was used to detect changes with time within each group. Data are expressed as median with upper and lower quartiles. $P < 0·05$ was considered significant.

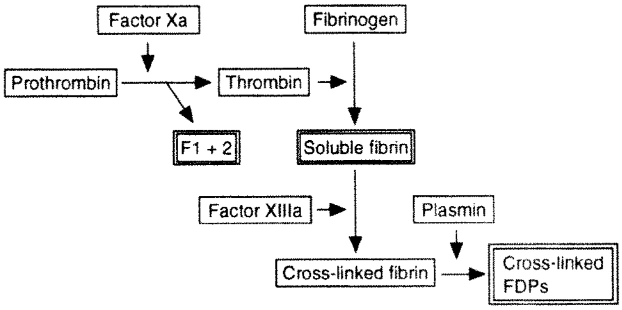


Fig. 1 Important pathways of coagulation and fibrinolysis. Markers of coagulation and fibrinolysis measured in the present study are shown in double-bordered boxes. F1 + 2, prothrombin fragment 1 and 2; factor Xa, activated clotting factor X; factor XIIIa, activated clotting factor XIII; FDPs, fibrin degradation products (detected by D-dimer antigen)

Results

Clinical data

The two groups were comparable with respect to age, sex, BMI and duration of operation (*Table 1*). Results of randomization and patient flow are shown in *Table 2*. Patient data were included in the analysis until the time of conversion to open operation. No statistical difference was found in conversion rates (P = 0·14). The time to complete disappearance of pain after discharge tended to be longer in the CLC group, but the difference was not statistically significant (8 *versus* 5 days; P = 0·23). However, the time to return to normal activity was significantly shorter in the GLC group (6 *versus* 8·5 days; P = 0·03).

Markers of coagulation and fibrinolysis

Plasma levels of F1 + 2 (*Fig. 2a*), D-dimer (*Fig. 2b*) and soluble fibrin (*Fig. 2c*) did not differ between the CLC and GLC groups at any of the perioperative sampling times ($P > 0·05$). F1 + 2 levels varied significantly in both groups ($P < 0·001$); after induction of anaesthesia they decreased, and then increased during operation, reaching a maximum

Table 1 Patient details

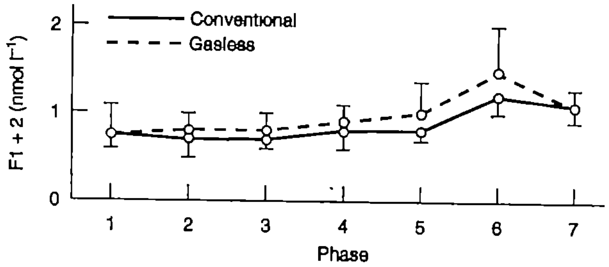
	Conventional laparoscopic cholecystectomy (*n* = 26)	Gasless laparoscopic cholecystectomy (*n* = 24)
Age (years)	52 (29–75)	49·5 (29–71)
Sex ratio (M : F)	8 : 18	7 : 17
Body mass index (kg m^{-2})	26 (20–30)	27 (23–30)
Length of operation (min)	78 (45–170)	102 (40–210)

Values are median (range)

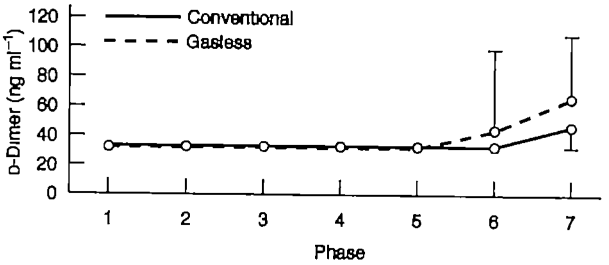
Table 2 Results of randomization and patient flow

	Conventional technique	Gasless technique
No. randomly assigned to treatment	26	24
Phase 2, after induction	26	24
Phase 3, after carbon dioxide insufflation or traction	26	23 (1)
Phase 4, 30 min after insufflation or traction	25 (1)	23 (3)
Phase 5, 10 min after exsufflation or traction	25	20
Phase 6, 4 h after extubation	24*	19*
Phase 7, 24 h after extubation	25	20

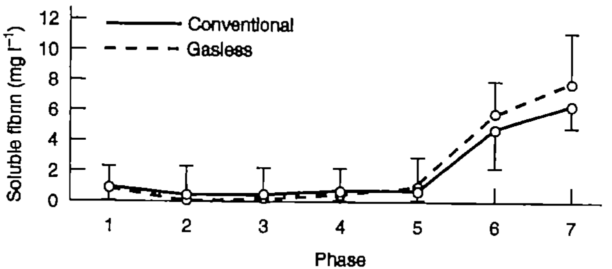
Values in parentheses are numbers of patients converted to an open procedure. *Missing value



a Prothrombin fragments 1 and 2



b D-dimer



c Soluble fibrin

Fig. 2 Plasma levels of a prothrombin fragment 1 and 2 (F1 + 2), **b** D-dimer and **c** soluble fibrin at various perioperative sampling times: phase 1, preoperative; phase 2, after induction of anaesthesia; phase 3, after carbon dioxide insufflation and traction, and introduction of the laparoscope; phase 4, 30 min after introduction of the laparoscope; phase 5, 10 min after exsufflation of carbon dioxide or release of traction; phase 6, 4 h after extubation; phase 7, 24 h after operation. Values are median with upper or lower quartiles

4 h after operation (phase 6). Soluble fibrin and D-dimer levels did not change significantly during operation in either group ($P > 0.05$), but after operation the levels increased significantly in both groups ($P < 0.001$).

Discussion

This study does not support the hypothesis that carbon dioxide pneumoperitoneum enhances the activation of coagulation and fibrinolysis associated with laparoscopic cholecystectomy. It appeared that the two laparoscopic methods activated the coagulation and fibrinolytic systems to approximately the same degree, as no differences between the two methods in levels of markers of coagulation and fibrinolysis were demonstrated in the perioperative period.

The magnitude of perioperative changes was similar to that in a previous study, which is noteworthy considering that the two studies differed in terms of their use of pharmacological thromboprophylaxis[1]. In the previous study, patients routinely received a low molecular weight heparin for thromboprophylaxis, whereas in the present study no pharmacological thromboprophylaxis was given to avoid any influence of anticoagulant effect on the marker levels. Instead, the patients wore thigh-length elastic compression stockings (Kendall TED®, Kendan, Vedbaek, Denmark) to prevent postoperative venous thromboembolism (VTE). None of the patients in these two studies developed clinical signs of VTE. In observational studies, the reported incidence of DVT after CLC ranges from 0·05 to 55 per cent[4–6].

It can be argued that insertion of the curved steel needles and traction on the abdominal wall in itself might affect the coagulation system, for example by inducing bleeding or disruption of subcutaneous tissues. Neither haematomas nor other complications were observed more frequently in the GLC group than in the CLC group, and no differences between the groups were found with respect to postoperative pain, analgesia or hospitalization, although the length of convalescence was significantly shorter in the gasless group than in the conventional laparoscopic group. The duration of operation in the GLC group tended to be longer than that in CLC group, reflecting a less optimal exposure of the operative field in the GLC group[14], which may mask a significant difference between the two groups.

The effects of abdominal distension with carbon dioxide are complex and may comprise direct mechanical compression effects, neurohumoral responses, and changes induced by absorbed carbon dioxide. It has been shown that plasma concentrations of adrenaline, renin–aldosterone and prolactin increase considerably after pneumoperitoneum and changes in position[15], but no results have been published regarding the effect on coagulation and fibrinolytic systems.

In conclusion, carbon dioxide pneumoperitoneum does not enhance the activation of coagulation and fibrinolysis associated with laparoscopic cholecystectomy. The coagulation and fibrinolytic systems are activated during and after gasless as well as conventional laparoscopic cholecystectomy.

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Original article

Outcome and resource utilization in gastroenterological surgery

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Background: A small minority of patients undergoing gastroenterological surgery are at high risk for postoperative complications, which may lead to prolonged hospital stay, disproportionate use of resources and increased mortality. The nature and frequency of, and predictive factors for, postoperative complications were studied and the impact of complications on resource utilization was assessed.

Methods: A prospective observational study was undertaken of 503 patients undergoing gastroenterological surgery in a tertiary care centre. The incidence of cardiorespiratory, infective and surgical complications was assessed. The need for reoperation, intensive care and length of hospital stay, readmission, death at 6 months and costs were evaluated.

Results: Some 235 patients (47 per cent) had at least one complication, most commonly delayed oral intake ($n = 70$). Complications were associated with cardiovascular disease, prolonged operation, high Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity, and increased number of Shoemaker's criteria. The length of hospital stay of patients with complications was longer than that of those without complications (11 *versus* 6 days). Morbidity resulted in a twofold increase in median costs.

Conclusion: High-risk patients could be identified by simple clinical criteria, although the commonly used risk criteria were not very sensitive. A reduction in postoperative complication rates would result in marked cost savings.

Presented in part to the 11th Annual Congress of the European Society of Intensive Care Medicine, Stockholm, Sweden, September 1998, and to the Biennial Congress of the Scandinavian Surgical Society, Turku, Finland, June 1999, and published in abstract form in *Intensive Care Med* 1998; **24:** S42, S43

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Introduction

Recovery from surgery is fast and uncomplicated in most patients and the overall mortality rate after non-cardiac surgery is approximately 1–2 per cent[1–3]. Several patient- and operation-related factors increase the risk of complications. Established risk factors include increasing age, impaired cardiovascular function and type of surgery[1,4–7]. In gastrointestinal surgery postoperative complications occur more frequently and the mortality rate is higher (4 per cent) than in many other surgical specialties[1,8–15]. Patients who develop complications and whose hospital stay is prolonged may consume a disproportionately larger share of the available resources[7,16]. Postoperative morbidity may not only increase the costs of care but also lead to prolonged sick leave and to permanent incapacity.

Recent studies suggest that preoperative screening may facilitate the selection of patients for appropriate perioperative management[15,17], and that perioperative interventions on high-risk patients undergoing major surgery may be beneficial and reduce the risk of death or the length of hospital stay[18,19]. Definitions of complications and risk factors related to gastroenterological surgery vary extensively[8,9,13,20,21]. The reported incidence of complications is also greatly dependent on patient selection[22]. Few reports have clarified the implications of complications for an individual patient or for resource utilization[23].

The aim of this study was to determine the nature and frequency of complications after gastroenterological operations, and to identify factors predictive of postoperative morbidity. The primary endpoint was to assess the impact of postoperative complications on resource utilization in

Table 1 Definition of complications[27]

Cardiorespiratory
Respiratory failure (mechanical ventilation >24 h)
Cardiac failure, cardiac index <2 litres per min per m^2 (treated first by fluid resuscitation and if no response by inotropic or vasoconstrictive medication)
Pulmonary oedema (radiological diagnosis)
Pleural fluid (radiographic diagnosis)
Acute myocardial infarction (electrocardiographic diagnosis)
Acute renal failure (need for haemofiltration)
Stroke with neurological symptoms
Pulmonary embolism, distal ischaemia (digital angiography and clinical diagnosis)
Deep venous thrombosis (phlebography)
Other cardiorespiratory
Surgical
Unexpected blood loss >0·5 litres during operation
Bowel perforation
Wound dehiscence
Postoperative bleeding (overt blood loss requiring >2 units transfusion with normal clotting profile)
Delayed oral intake (intravenous fluids >1 week owing to postoperative ileus)
Anastomosis leakage
Other surgical
Infective
Sepsis (pyrexia >38°C and septic focus or positive blood culture)
Postoperative peritonitis (clinical diagnosis)
Abdominal abscess (ultrasonography, computed tomography or operative diagnosis)
Necrotizing fasciitis
Wound infection (positive wound swab culture)
Pneumonia (radiological diagnosis)
Chest infection (e.g. mediastinitis, empyema)
Urinary tract infection
Disseminated intravascular coagulation
Other infectious complication

terms of length of hospital stay, need for intensive care and costs.

Patients and methods

This was a prospective follow-up study with no interventions. The ethics committee of Kuopio University Hospital (KUH) approved the study and informed consent was obtained from each patient or the near relatives. KUH serves as a tertiary referral centre to a population of 870 000 inhabitants in eastern Finland. The study population consisted of patients aged 16 years or more, admitted during a 12-month period between 1996 and 1997, and having a laparotomy for a gastroenterological disease. Those who had an appendicectomy, a transrectal procedure or inguinal herniotomy were excluded. If the patient had more than one operation, the first procedure was taken into account. All patients were treated according to the routine practice of the attending anaesthesiologists and surgeons.

Data were collected prospectively for preoperative diseases, American Society of Anesthesiologists (ASA) status[24], Shoemaker's criteria[25], Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM)[26], and type of surgical procedure. An operation was classified as urgent if the patient was considered to need an operation within 24 h after hospital admission. Follow-up lasted for 6 months after discharge. Complications were predefined (*Table 1*, *Fig. 1*)[27]. The impact of complications (*Fig. 2*) was assessed by an anaesthesiologist (M.L.) and a gastrointestinal surgeon (P.M.). The change from the preoperative health status was taken into account. Because factors other than purely medical variables may influence discharge from hospital, each patient was assessed individually. As a guideline, the usual length of hospitalization was taken as 7 days for exploratory laparotomy, 5 days for ventral hernia operation, 11 days for a procedure involving the oesophagus, stomach and duodenum, 10 days for an intestinal procedure, 12 days for a rectal procedure, 7 days for stoma formation, 7 days for open cholecystectomy, 12 days for pancreatic resection and 7 days for other procedures.

Cost accounting

The communities in the KUH catchment area finance the hospital. KUH receives a government subsidy for education

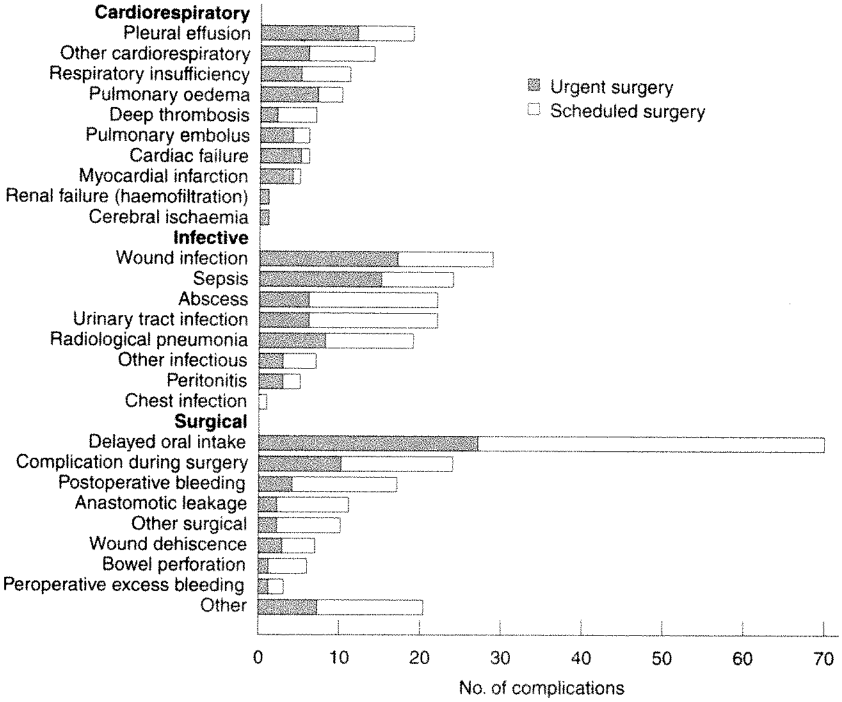


Fig. 1 Occurrence of cardiorespiratory (n = 64), infective (n = 107), surgical (n = 123) and other complications[27] in 503 patients. Patients could have complications in more than one category

and research. The calculation of costs was based on the internal hospital cost accounting system, under which each department within the hospital sells services to other departments on a non-profit basis. The prices of these services are determined by the total costs of a service per patient. The costs were calculated by totalling the costs of anaesthesia, surgery, intensive care unit (ICU), operating room, all laboratory tests, clinical radiology, drugs, nutrition and costs of hospital patient-days accumulated per patient during the same hospital stay. This method can be regarded as a modified bottom-up method. The costs were obtained from the hospital's computerized database. ICU costs were obtained from a clinical information management system (Clinisoft CIMS®; Datex-Ohmeda, Helsinki, Finland) and calculated as follows: cost per therapeutic intervention scoring system (TISS) score = annual ICU expenditure/total accumulation of TISS scores; costs per patient = patient TISS score accumulation × cost of one TISS score. In 1996–1997 the cost of one TISS point was €33[28].

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 7.5 program (SPSS, Chicago, Illinois, USA). Data are expressed as median (range) unless otherwise stated. Differences between groups were calculated by χ^2 test, Student's unpaired t test or Mann–Whitney U test as appropriate. No correction for multiple comparisons was performed. Logistic regression analysis was carried out to study the independent contribution of variables on the development of complications. Youden's index[29] (sensitivity + specificity − 1) was chosen for the best cut-off value. Statistical significance was defined as $P < 0.05$.

Results

Demographics

The study population consisted of 503 patients (236 men and 267 women) who underwent 566 operations. Six hundred and ninety-eight patients fulfilled the inclusion criteria and 195 were excluded owing to patient refusal or failure to obtain consent. These patients did not differ from the study patients with respect to age, sex, ASA status, length of hospital stay or hospital mortality rate. Descriptive data according to the site of operation are presented in *Table 2*. Fifty-six patients were classified as having ASA status I, 179 as ASA II, 232 as ASA III, 32 as ASA

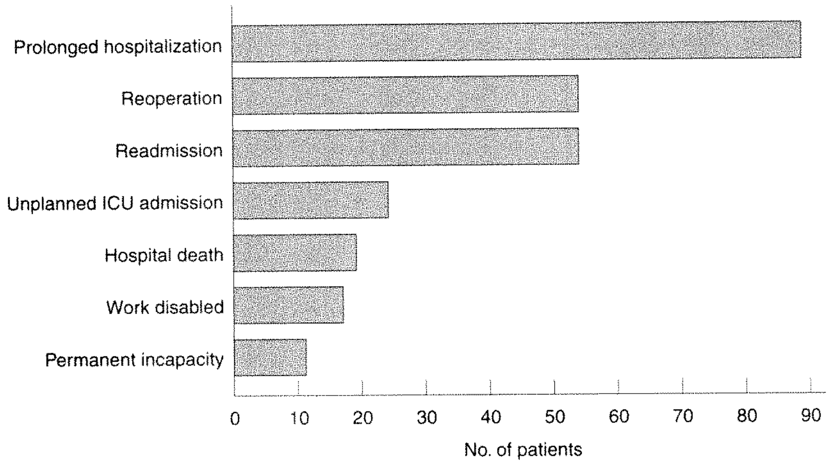


Fig. 2 Impact of complications on the 503 study patients. Work disabled accounts for patients with prolonged sick leave or inability to work as a consequence of complications. ICU, intensive care unit

Table 2 Proportion of urgent operations, patient age and length of operation according to the site of operation

Site or operation	No. of patients*	No. of urgent operations*	Age (years)†	Length of operation (min)‡
Exploratory laparotomy	58	38 (66)	59(18)	73 (13–382)
Ventral hernia	45	16 (36)	61(13)	91 (18–263)
Oesophagus, stomach and duodenum	40	8 (20)	59(14)	132 (21–394)
Intestine	83	32 (39)	62(16)	150 (45–370)
Rectum	48	4 (8)	64(15)	187 (80–405)
Stoma formation	39	15 (38)	57(17)	122 (39–272)
Biliary tract	158	88 (56)	61(15)	104 (20–336)
Pancreas (resection)	14	0 (0)	60(16)	302 (60–504)
Other	18	4 (22)	54(12)	165 (55–497)
All	503	205 (41)	61(16)	119 (13–504)

*Values in parentheses are percentages; values are †mean(s.d.) or ‡median (range)

IV and four patients as ASA V. No Shoemaker's criteria were present in 279 patients, 135 had one criterion and 89 had two or more criteria. The median POSSUM score was 21 (10–47). There were 272 patients with a chronic cardiovascular disease (coronary heart disease, heart failure, rhythm disturbance, hypertension or cerebrovascular disease). Sixty-seven patients had a chronic respiratory disease.

Morbidity and mortality

A total of 235 patients had at least one complication. One-quarter of patients had a surgical complication, either functional or mechanical, one-fifth suffered from infective complications and 13 per cent had a cardiorespiratory complication (*Fig. 1*). Surgical and infective complications were most common after rectal operations (*Table 3*). The total number of complications was 376; 166 patients had one complication, 41 had two and 30 had three or more complications.

In 173 patients complications led to increased resource consumption or hospital death (*Fig. 2*). Thirteen patients died in hospital during the same hospitalization, 19 patients within 30 days and 46 within 6 months of the first operation.

Factors associated with complications

Factors associated with complications are shown in *Table 4*. Fourteen of the 17 patients who had pre-existing cardiovascular disease and who underwent rectal operation developed complications. The presence of chronic respiratory disease did not increase the occurrence of complica-

Table 3 Occurrence of complications according to the site of operation

Site or operation	No. of patients	No. of patients with complications*			
		Any	Cardiorespiratory	Infective	Surgical
Exploratory laparotomy	58	31 (53)	10	11	11
Ventral hernia	45	15 (33)	1	6	9
Oesophagus, stomach and duodenum	40	18 (45)	10	6	12
Intestine	83	44 (53)	12	20	24
Rectum	48	30 (62)†	3	17	18
Stoma formation	39	19 (49)	3	8	15
Biliary tract	158	62 (39)‡	21	30	25
Pancreas (resection)	14	8 (57)	1	4	5
Other	18	8 (44)	3	5	4
All	503	235 (47)	64	107	123

Values in parentheses are percentages. *Patients could have complications in more than one category. The frequency of complications was †higher or ‡lower than that in all remaining patients ($P < 0{\cdot}05$, χ^2 test)

Table 4 Preoperative and operation-related factors among patients with and without postoperative complications

	No complication ($n = 268$)	Complication ($n = 235$)	*P*
Age (years)*	58(16)	64(15)	0·018§
Coronary heart disease	46	67	0·002¶
Heart failure	11	21	0·027¶
Diabetes	24	39	0·010¶
Duration of operation (min)†	104 (13–394)	139 (15–504)	0·005**
Duration of intraoperative hypotension (min)†‡	5 (0–220)	10 (0–270)	0·004**
Blood loss during surgery (ml)†	200 (0–7000)	300 (0–32 000)	0·001**

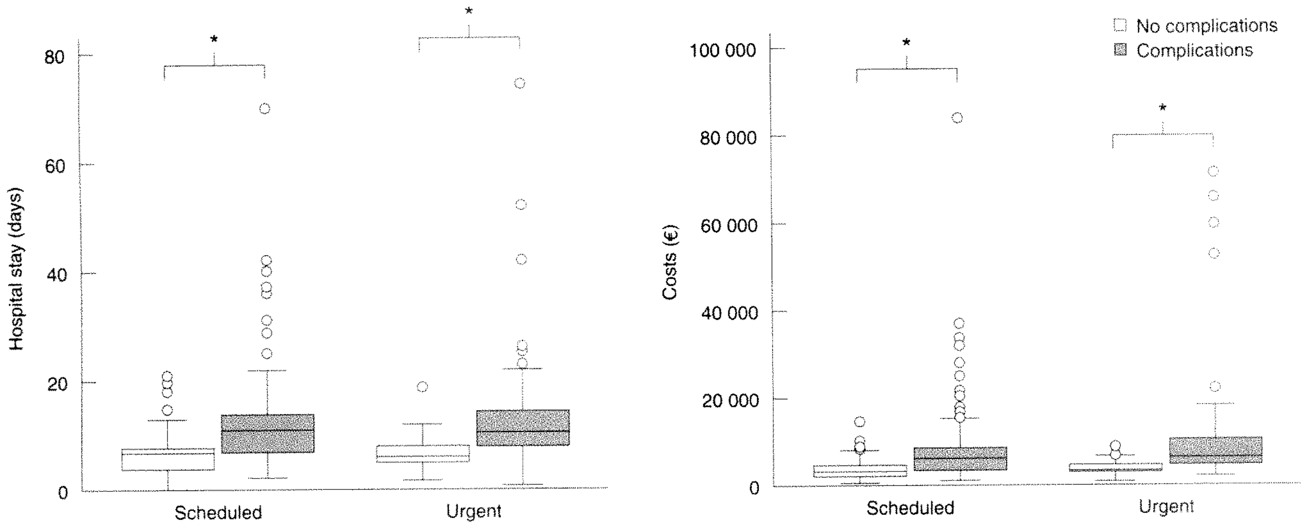
Values are *mean(s.d.) or †median (range). ‡Systolic arterial blood pressure less than 100 mmHg. § Student's unpaired *t* test, ¶χ^2 test, **Mann–Whitney *U* test

tions. One hundred and forty-one patients (47 per cent) undergoing elective surgery and 94 (46 per cent) of those who had an emergency operation had complications. The difference between these groups was not significant. Patients with complications had a greater number of Shoemaker's criteria and higher POSSUM scores than those with uncomplicated postoperative recovery (1 (0–6) *versus* 0 (0–3) and 24 (10–47) *versus* 19 (10–44) respectively; $P < 0{\cdot}001$). In a logistic regression analysis containing the variables listed in *Table 4*, as well as chronic respiratory disease, number of Shoemaker's criteria and rectal surgery as independent variables, only the number of Shoemaker's criteria ($P < 0{\cdot}001$) and the length of operation ($P < 0{\cdot}01$) were significant predictors for complications. The sensitivity and specificity of ASA status, Shoemaker's criteria and POSSUM in identifying patients who developed postoperative complications are presented in *Table 5*.

Resource allocation

The length of hospital stay after operation was 8 (0–74) days. The length of stay of patients with complications was longer than that for those without complications (11 (1–74) *versus* 6 (0–21) days; $P < 0{\cdot}001$). The 235 patients (47 per cent) who had a complicated recovery accounted for 3332 hospital patient-days, or 67 per cent of all patient-days of the study patients. The 119 patients (24 per cent) whose hospital stay lasted 13 days or longer consumed half of all hospital patient-days. Of these, 105 patients had complications. Costs per patient among patients with complications were higher than costs among those without complications (€6551 (1527–83 869) *versus* €3638 (896–14 849); $P < 0{\cdot}001$) after both scheduled and urgent surgery (*Fig. 3*). The urgency of operation did not affect costs in different complication categories (*Fig. 4*). The influence of complications on length of stay and costs according to the site of operation is presented in *Table 6*.

Thirty-eight patients were admitted to the ICU. Eleven of these patients were already being treated in the ICU before the first operation and 27 were admitted to the ICU after the first operation or later during their postoperative hospital stay. Three of these 27 patients had a scheduled ICU admission after surgery and had no complications. Six of the 24 patients who had an emergency admission to the



a Length of stay

b Costs

Fig. 3 Impact of the urgency of operation on **a** length of hospital stay and **b** costs among patients with complications or an uncomplicated recovery after scheduled (n = 298) and urgent (n = 205) surgery. Horizontal lines represent median values and boxes denote interquartile range; circles represent extreme cases. *P < 0·001 (Mann–Whitney U test)

Table 5 Sensitivity and specificity of the American Society of Anesthesiologists physical status classification[24], number of Shoemaker's criteria[25] and the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity [26] in identifying patients who developed postoperative complications

	Cut-off	Sensitivity (%)	Specificity (%)
ASA status	≥ 3	63	56
No. of Shoemaker's criteria	≥ 1	55	65
POSSUM score	≥ 19	74	48

ASA, American Society of Anesthesiologists; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity

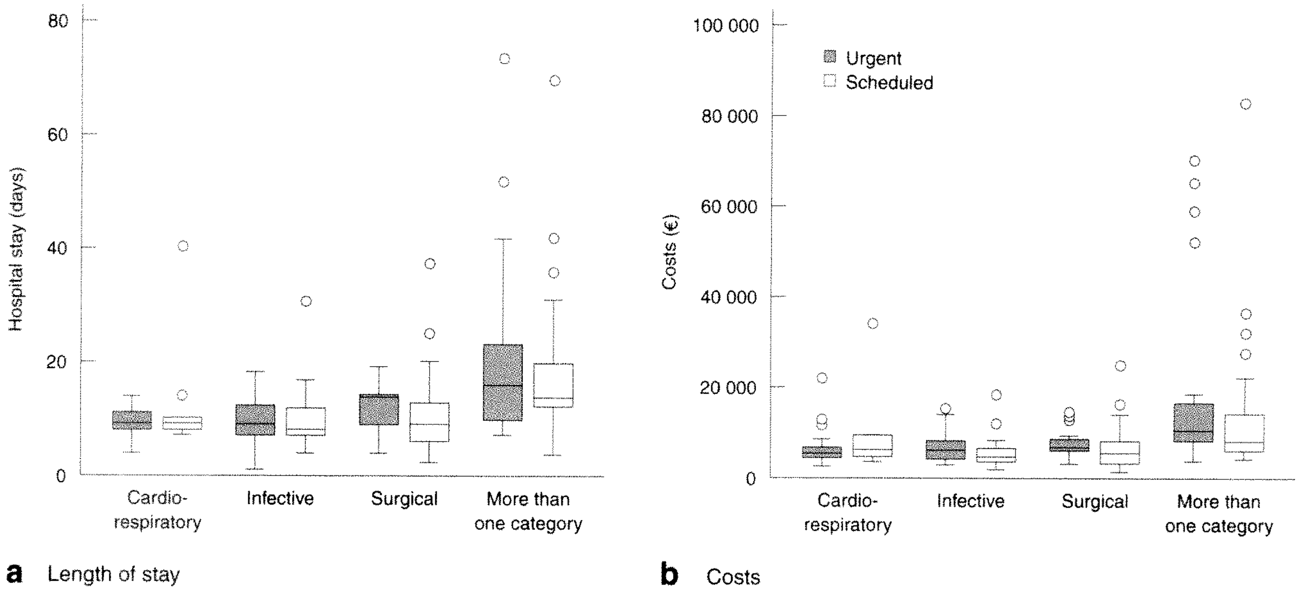
ICU died during their stay in hospital. The ICU stay of 24 patients with a postoperative emergency ICU admission lasted for 2·2 (0·3–70) days and the median cost of the ICU stay was €2748 (762–178 136). The ICU costs represented one-third of all costs for these patients.

Discussion

The main findings of this study were that approximately one-half of patients undergoing gastroenterological surgery had postoperative complications, which resulted in a twofold increase in the length of hospital stay and costs of care.

Complications have been reported to occur in up to two-thirds of patients undergoing gastroenterological surgery, presumably because of wide definitions[13]. Cardiopulmonary complications occurred in one-fifth of patients in a study by Pedersen *et al.*[10]. Cardiovascular and respiratory complications occurred together in one-third of patients described by Lawrence *et al.*[8]. The results of the present study are in accordance with these findings. Of 64 patients with cardiorespiratory complications, 18 patients had both cardiovascular and respiratory problems. In a study by Hall and Brooks[13] the incidence of infectious complications (22 per cent) and wound infection (6 per cent) corresponded with those of the present study, while parenteral nutrition was required less frequently (6 per cent). Variable definitions and heterogeneity between patients make comparison between studies difficult. For practical reasons blinding of the study was not considered feasible and it remains unclear how blinding would have affected the results. In addition, the fact that no protocols for the management of complications were used may have caused bias because clinicians were aware of the study.

Complications were associated with easily recognizable clinical factors, such as increasing age, cardiovascular diseases and a prolonged operation, and occurred most often with rectal surgery as noted previously[4–6,10]. Shoemaker's criteria have been used mainly to select patients for therapeutic trials[25,27], and have not been designed specifically for risk prediction. Nevertheless, the ability of these rather pragmatic and readily available



a Length of stay **b** Costs

Fig. 4 **a** Length of hospital stay and **b** costs after scheduled and urgent surgery among patients with purely cardiorespiratory (*n* = 26), infective (*n* = 55) or surgical (*n* = 70) complications and among those with complications in more than one category (*n* = 65). Horizontal lines represent median values and boxes denote interquartile range; circles represent extreme cases (Mann–Whitney *U* test)

Table 6 Hospital stay after operation and costs for different operation types in patients with (*n* = 235) and without (*n* = 268) post-operative complications

Site or operation	No. of patients	Hospital stay (days)			Total costs (€)		
		No complication	Complication	*P**	No complication	Complication	*P**
Exploratory laparotomy	58	6 (2–19)	10 (1–25)	< 0·001	3698 (1603–14 849)	6214 (2563–22 431)	< 0·001
Ventral hernia	45	3 (1–8)	8 (4–20)	< 0·001	1743 (916–5375)	3069 (1696–16 582)	< 0·001
Oesophagus, stomach and duodenum	40	7 (1–11)	10 (4–70)	0·002	4405 (1792–6260)	9152 (1788–83 869)	< 0·001
Intestine	83	8 (0–21)	12 (1–42)	< 0·001	4233 (896–10 787)	6529 (2308–71 019)	< 0·001
Rectum	48	7 (5–15)	13 (7–36)	< 0·001	4330 (2537–10 752)	7049 (2638–27 721)	< 0·001
Stoma formation	39	6 (4–12)	13 (5–37)	< 0·001	3758 (2132–6594)	7987 (2859–25 003)	< 0·001
Biliary tract	158	6 (2–18)	9 (3–74)	< 0·001	3445 (1384–9401)	5428 (1527–65 404)	< 0·001
Pancreas (resection)	14	8 (6–12)	11 (2–19)	0·295	6678 (4337–8266)	9168 (4671–14 205)	0·156
Other	18	8 (3–10)	11 (7–20)	0·008	4393 (1542–8344)	8600 (3695–20 660)	0·008

Values are median (range). *Mann–Whitney *U* test

criteria to predict complications was confirmed in the present study. A further argument for the evaluation of these criteria is the lack of widely accepted instruments for predicting complications in gastroenterological surgery. In a study by Boyd *et al.*[27] the mortality rate was 14 per cent if a patient had two or more Shoemaker's criteria, compared with 11 per cent among this patient group in the present study. However, Shoemaker's criteria were not very sensitive in identifying high-risk patients. Complications were clearly associated with a higher POSSUM rating, but the low specificity limits its value in clinical practice. A modification of POSSUM, the Portsmouth POSSUM equation, may provide a more accurate prediction[30].

Postoperative complications caused a major increase in resource utilization, most commonly owing to prolonged hospitalization. Previous studies have shown an approximately twofold increase in the length of stay or costs due to complications after abdominal[9] or cardiac[23] surgery, and in high-risk surgical patients in general[19]. Lawrence *et al.*[9] reported that hospital stay was longer after pulmonary than cardiac complications among patients undergoing abdominal surgery. The costs depend on various clinical practices and comparison between studies is difficult[31]. After colorectal surgery the excess cost has been estimated to be €2131 and after cholecystectomy €1139 per infection[31,32]. In the present study the variation in cost and length of stay within various types of surgery was great. Death, however, may be the most costly ultimate outcome[23]. There were no major differences in the length of stay or costs between the type of complications and therefore any complication may be relevant. If the complication rate could have been halved by an intervention in all patients with two or more Shoemaker's criteria ($n = 89$), 446 patient-days and €260 858 could have been saved.

In a previous study of patients undergoing digestive or hepatobiliary surgery, 6 per cent of patients were admitted in the perioperative period to the ICU[13]. In the present study 8 per cent of patients were treated in the ICU during some phase of their disease, although only a small proportion (2 per cent) received preoperative fluid therapy in the ICU or in the recovery room. Preoperative optimization of oxygen delivery in properly selected patients undergoing major surgery reduces the number of postoperative complications[19,33], improves survival and reduces costs[16].

In conclusion, while half of patients recover without complications and can be managed normally, the remainder develop complications that double resource consumption and costs. There is evidence that the outcome after high-risk surgery may be improved by quite simple treatment interventions. Simple criteria for identification and proper tracking of high-risk patients are desirable. Further studies aimed at improving the outcome for high-risk patients by treatment interventions are needed.

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The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

The Seldinger technique for difficult transurethral catheterization: a gentle alternative to suprapubic puncture (*Br J Surg* 2000; 87: 1729–30)

Letter 1

Sir

It is our experience that a guide wire cannot always be successfully forwarded into the bladder because the guide wire coils itself within an enlarged prostate or lodges in a urethral stenosis. In this situation the key to success lies in the bedside use of the flexible cystoscope[1]. The technique is simple, safe, fast and highly reliable. If the prostate is enlarged the fibroscope can be guided into the bladder under direct vision and a guide wire passed through the operative channel and coiled into the bladder. The fibroscope is then withdrawn and a Foley catheter with the tip cut off is easily advanced into the bladder. If a urethral stenosis exists, the small urethral opening can be easily seen and a guide wire negotiated through it until it reaches the bladder. The fibroscope is then withdrawn and a coaxial urethral dilation with a Finlayson set easily performed to a calibre that permits the insertion of a Foley catheter (with the tip cut off) over the guide wire. Whenever possible blind manoeuvres should be avoided and the use of the flexible cystoscope allows success without damage to the urethral mucosa[1].

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1 Carmignani G, De Stefani S, Maffezzini M, Simonato A, Capone M. Special applications in use of flexible cystoscope. *Urology* 1991; **38:** 192–3 (Letter).

Letter 2

Sir

This paper appears to support repeated urethral manipulation when catheterization by this route has failed. Minimal morbidity is claimed and the policy is supported above the option of suprapubic catheterization. A follow-up period of any significance is not reported and only early postoperative complications were sought. Previous studies have shown that urethral stricture formation, an important cause of urological morbidity following cardiac surgery, may only become apparent up to 2 years after surgery[1]. While the incidence of stricture formation following both cardiac and aortic surgery can be reduced by the use of silicone rather than latex catheters[1], multiple attempts at catheterization can only increase the risk of urethral trauma and long-term complications. Previous randomized studies have also shown that suprapubic catheterization at the time of surgery is indeed superior to the urethral route, in terms of lower postoperative morbidity, postoperative discomfort and a lower incidence of bacteriuria[2,3].

We would advocate a single attempt at urethral catheterization with a silicone catheter. If this fails a suprapubic catheter should be inserted, for both the short- and long-term benefit of the patient.

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Author's reply

Sir

We and others have seen bleeding complications after suprapubic puncture following unsuccessful transurethral catheterization. The risk seems particularly high in those patients receiving heparin, those presenting with coagulation disorders or those requiring immediate postoperative anticoagulation. We believe that our technique provides a clear advantage over suprapubic puncture, owing to its less invasive character.

We acknowledge that urethral strictures can occur after urethral catheterization, but have not yet encountered this complication. We agree that an appropriate choice of catheter is important in preventing urethral strictures. The small sized 6 Fr silicone or polyurethane catheters used in our insertion technique should further avoid any urethral trauma

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Gender differences in the longitudinal pressure profile of the anal canal related to anatomical structure as demonstrated on three-dimensional anal endosonography (*Br J Surg* 2000; 87: 1674–9)

Sir

The 'misimpression' of a shorter anterior external anal sphincter (EAS) implies a greater relative contribution by the posterior puborectalis and since this distinction has not been made in reported dissections[1,2] (given that there is a clear plane of cleavage between the two muscles[3]), this needs to be revisited in the dissecting room.

The manometric findings in this paper should be viewed with caution, since the demonstration of muscle in a region of the anal canal does not prove that it is functionally contributing to the recorded pressure. We found manometric differences between continent and incontinent patients after internal sphincterotomy for topical-resistant chronic anal fissure where there were no differences in postoperative resting high pressure zone (HPZ) lengths or sphincterotomy extent[4]. We have also shown constitutively shorter preoperative subcutaneous EAS/internal anal sphincter (IAS) overlap on endoanal magnetic resonance imaging in patients with chronic anal fissure[5] without differences in resting HPZ or IAS lengths. These findings do not explain the results of Williams and colleagues that part of the HPZ extends below the IAS termination.

Continence is more complicated than observable muscle bulk or disposition, although these are important. The finding of parametric variations in the rectoanal inhibitory reflex in different anorectal conditions is one factor affecting continence, independent of anatomy[6]. This has important medicolegal implications, since patients should be warned that functional outcome following minor anorectal surgery can still be impaired in the absence of inadvertent sphincter injury or reconstructed variability in sphincter disposition.

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Author's reply

Sir

Abel and BeerGabel raise several important points in their letter. We have found high definition magnetic resonance imaging the easiest and most revealing method to demonstrate the anatomy of the striated components of the sphincter (unpublished data) and agree that this frequently shows a plane of cleavage between one or more of the external sphincter divisions. This is seldom apparent on endosonography, even with multiplanar three-dimensional views, as the primary image is derived from thin axial sections oblique to the plane of cleavage, so that this is usually obscured.

The central theme of our article was to determine the relationship between the anal musculature and manometric profile in both sexes. The study was not designed to separate out the effects of the different components, i.e. the internal from the external sphincters, but we have implied a causal relationship between structure and function, and believe we have highlighted a potentially greater sphincteric role for the puborectalis than previously recognized.

We accept the caution of taking too simplistic an approach to this difficult subject, and note with interest their latest work. The lack of change in resting pressure following sphincterotomy is intriguing, and emphasizes the need for further research using techniques we have both described if we are to obtain a better understanding of how structure relates to function and so improve the surgery of anal disorders.

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Rectal adenocarcinoma with liver metastases: management of the primary tumour (*Br J Surg* 2001; 88: 163–4)

Sir

We agree with the general principles outlined in this excellent article but also wish to emphasize that the decision about resectability of colorectal liver metastases should be made in consultation with an experienced hepatobiliary surgeon. More complex staging investigations are usually required, including computed tomographic portography[1] and/or magnetic resonance imaging. Laparoscopy with laparoscopic ultrasonography[2] and positron emission tomography may also have a role in selected patients. Importantly, the proportion of patients deemed suitable for hepatic resection has increased through the use of several novel techniques. These include neoadjuvant chemotherapy to downstage disease[3], portal vein embolization to hypertrophy the small hepatic remnant[4], and staged liver resections. In this way, we have resected radically a number of patients previously deemed inoperable. Finally, intraoperative or percutaneous biopsy of potentially resectable colorectal liver metastases is both unnecessary and risks tumour seeding. This practice should be discouraged.

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1 Moran BJ, O'Rourke N, Plant GR, Rees M. Computed tomographic portography in preoperative imaging of hepatic neoplasms. *Br J Surg* 1995; **82:** 669–71.
2 John TG, Greig JD, Crosbie JL, Miles WF, Garden OJ. Superior staging of liver tumors with laparoscopy and laparoscopic ultrasound. *Ann Surg* 1994; **220:** 711–9.
3 Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D *et al.* Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996; **224:** 509–20.
4 Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. *Br J Surg* 2001; **88:** 165–75.

Epidemiology of abdominal aortic aneurysms in the Asian community (*Br J Surg* 2001; 88: 382–4)

Sir

We similarly serve an area with a high proportion of Asian patients. In the last 7 years only one Asian patient has been operated on for aortic aneurysmal disease, a 63-year-old man with a 5·5 cm aneurysm. However, he had been resident the UK for over 30 years. I wonder if this may be a case of environmental factors taking over from genetic predisposition? It will be interesting to see if there is a change in incidence amongst Asian residents in the UK in the future.

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Randomized trial of needlescopic *versus* laparoscopic cholecystectomy (*Br J Surg* 2001; 88: 45–7)

Letter 1

Sir

Although commonly used, we feel that needlescopic is inappropriate terminology for this procedure because the only difference between the two techniques is the diameter of the instruments. Laparoscopic cholecystectomy using fine-calibre instruments may be a more convenient description. The authors concluded that the reduction in postoperative pain achieved by fine-calibre instruments was because of the smaller wounds. However, pain after laparoscopic cholecystectomy has several components: parietal, visceral and referred pain. The stretching of the abdominal cavity[1], the degree of peritoneal inflammation[2], and phrenic nerve irritation caused by residual carbon dioxide[3] may also produce pain. Visceral pain accounts for most of the pain experienced after laparoscopic cholecystectomy[2]. Were the two groups similar in terms of mean abdominal pressures, frequency and intensity of abdominal contamination with bile or blood, and mean CO_2 used, to compare the pain perception?

We perform laparoscopic cholecystectomy with only three ports (by eliminating the mid-axillary port) and using conventional instruments. Elimination of a 5-mm port makes the total length of incision about the same as the fine-calibre group. In our opinion, the additional expense and lack of effectiveness do not make it worthwhile to use fine-calibre instruments during laparoscopic cholecystectomy. What was the indication for conversion to laparoscopic cholecytectomy in three patients in the needlescopic group?

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1 Joris J, Thiry E, Paris P, Weerts J, Lamy M. Pain after laparoscopic cholecystectomy: characteristics and effect of intraperitoneal bupivacaine. *Anesth Analg* 1995; **81:** 379–84.
2 Colbert ST, Moran K, O'Hanlon DM, Chambers F, Moriarty DC, Blunnie WP. An assessment of the value of intraperitoneal meperidine for analgesia postlaparoscopic tubal ligation. *Anesth Analg* 2000; **91:** 667–70.
3 Jackson SA, Laurence AH, Hill JC. Does post laparoscopy pain relate to residual carbon dioxide? *Anaesthesia* 1996; **51:** 485–7.

Letter 2

Sir

The authors state that needlescopic cholecystectomy was no more difficult than the standard laparoscopic procedure but this seems to be based on their findings that there was no difference in the duration of surgery and in complications between the two groups. However, three of 37 of the needlescopic group needed conversion to the standard laparoscopic procedure. I do not think therefore that the authors can claim that the needlescopic procedure is no more difficult than the standard laparoscopic cholecystectomy.

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Author's reply

Sir

Needlescopic is only one of many terms that describe fine-calibre instruments. Other terms include 'microlaparoscopic' and 'minilaparoscopic'. These instruments handle differently to normal laparoscopic instruments and can bend with excessive force. We agree that pain after laparoscopic cholecystectomy is due to multiple factors. In both the needlescopic and laparoscopic groups, the mean abdominal gas pressure was maintained at 12 mmHg. There was no difference in frequency of abdominal contamination with bile and there was no difference in operative duration (as a measure of the mean CO_2 used). By randomizing patients to either group and maintaining standard operative procedures, we believe that the differences in pain perception could be due to the different techniques used.

The reason for converting three needlescopic patients was due to the presence of thickened gallbladders, even though the operations were performed in the elective setting. We believe that the needlescopic procedure is suitable in selected patients with non-inflamed chronic cholecystitis. In patients with thickened or acutely inflamed gallbladders the needlescopic approach will be difficult and will not confer much advantage.

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The National Institute for Clinical Excellence and hernia repair

Sir

The National Institute for Clinical Excellence (NICE) in the UK has recently issued guidelines on hernia repair[1]. As with all NICE guidelines they are made on the best available evidence and this particular set will be due for review in 2003. However, there is the potential for guidelines to become media and political dogma. The document states that 'For repair of primary inguinal hernia, open (mesh) should be the preferred surgical procedure'. In a survey of 60 consultants in southern England undertaken in 2000 we found that 32 per cent of consultants who used the open mesh repair in men did not always place a mesh in women. At first sight this seems to be sexist and against current guidelines. However, in the large trials by Lichtenstein in America on open mesh repair, gender differences were not examined. Some of the largest trials have involved only men[2]. The consultants who did not use mesh in women gave the reason that women invariably have an indirect inguinal hernia and, where the tissues of the posterior wall of the inguinal canal are strong, a case can be made for simple obliteration of the canal without mesh insertion. In Lichtenstein's trials infection of mesh repair occurred less and recurrence rates were lower than with the Shouldice repair[3]. It may well be, therefore, that these surgeons are right and certain women do not need a mesh. Perhaps we should study gender differences in hernia repair or risk going against current guidelines and become politically incorrect.

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1 NICE guidelines. Technology Appraisal Guidance Number 18. Guidance on the Use of Laparoscopic Surgery for Inguinal Hernia. London: Department of Health Press Office, January 2001.
2 Janu PG, Sellers KD, Mangiante EC. Mesh inguinal herniorraphy: a 10-year review *Am Surg* 1997; **63**: 1065–9, discussion 1069–71.
3 Shulman AG, Amid PK, Lichtenstin IL. The safety of mesh repair of primary inguinal hernias: results of 3019 operations from five diverse surgical sources. *Am Surg* 1992; **58**: 255–7.

Probiotics (*Br J Surg* 2001; 88: 161–2)

Sir

Our understanding of the composition and interactions of gut bacteria remains limited despite the increasing data showing a reduction in inflammation and symptoms in experimental and clinical enterocolitis treated with probiotics. These results strengthen the hypothesis that bacteria are involved in the aetiology of inflammatory bowel disease (IBD)[1]. It is unlikely that a single probiotic will be effective in everyone with IBD since different bacteria may be contributing to the persistence of intestinal inflammation in different patients. Different species of probiotic bacteria may be the dominant protective species in each patient and as the author comments, not all probiotics are likely to be equally effective in all patients.

We have shown that treatment with *Lactobacillus plantarum* species 299 stabilizes the gut mucosal barrier in patients with ulcerative colitis and in the interleukin 10 knockout mouse model of colitis[2,3]. There was also a reduction in markers and indices of disease activity in patients with ulcerative colitis[3].

These findings suggest that probiotic therapy, by reducing intestinal inflammation, results in a stabilization of the gut mucosal barrier and a consequent reduction in the systemic inflammatory response in patients with ulcerative colitis. Further research is required to elucidate the mechanisms by which these bacteria reduce inflammation and improve symptoms.

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1 Sartor RB. Review article: role of the enteric microflora in the pathogenesis of intestinal inflammation and arthritis. *Aliment Pharmacol Ther* 1997; **11:** 17–23.
2 Kennedy RJ, Hoper M, Weir H, Deodhar K, Erwin P, Sloan J *et al.* Probiotic therapy stabilizes the gut mucosal barrier in the interleukin 10 knockout model of colitis. *Br J Surg* 2000; **87:** 669–70 (Abstract).
3 Kennedy RJ. The effect of *Lactobacillus plantarum* species 299 on intestinal inflammation and associated gut mucosal barrier dysfunction. MD Thesis. The Queen's University of Belfast, 2000.

Duplicate text

You may wish to read the following reviews:

1 Bennett IC, Gattas M, Teh BT. The genetic basis of breast cancer and its clinical implications. *Aust N Z J Surg* 1999; **69**: 95–105.

2 Sakorafas GH, Tsiotou AG. Genetic predisposition to breast cancer: a surgical perspective. *Br J Surg* 2000; **87**: 149–62.

Plagiarism is the taking and using of another's thoughts, ideas or writings, without due acknowledgement. The editors have written to the authors of the above papers; paper 1 was published before the submission of paper 2 to *BJS*.

Drs Sakorafas and Tsiotou reply that they intended to produce a review article to describe 'what genetic predisposition for breast cancer means for the clinician and how these high risk women should be managed'. With regard to the paper previously published by Bennett *et al.* they feel that this represents 'a significant, clinically orientated contribution to the field of breast cancer and ... included it in the list of references'. They are also of the opinion that 'some similarities between the different review articles are to be expected'. Dr Bennett writes 'The article by Sakorafas and Tsiotou contains multiple sentences and paragraphs which have been directly copied from our review article and with ... only two references to our paper'.

The editors estimate 10 per cent text identity between these articles. As a future guide we suggest that authors err on the side of caution for attribution. If you wish to use that dramatic concluding sentence from a paper by another author then use it like this – 'Surgery is the only effective treatment for Crohn's disease(reference number)'. The quotes show that you have lifted the sentence verbatim from the reference work, while the reference number gives due acknowledgement to the original authors. If you *must* use a significant number of sentences from someone else's work, be sure to make adequate acknowledgement, either by repeated use of the same reference number or (perhaps better) by providing a formal footnote acknowledgement at the end of your paper, ideally with the blessing of the original author(s) and publisher. This is what is expected if you use an illustration or table – no less is expected for text.

J. R. Farndon
Joint Editor

Book reviews

Lymphatic Mapping and Probe Applications in Oncology

O. E. Nieweg, R. Essner, D. S. Reintgen, J. F. Thompson

235 × 155 mm. Pp. 378. Illustrated. 2000. New York: Marcel Dekker. $175·00.

The concept of lymphatic mapping and the sentinel node has swept over surgical oncology. Some of this innovation is evidence based; some is fashion. Any publication that brings together the basic concepts and available clinical evidence is welcome. But how informative is this book that comes from centres in Holland, the USA and Australia? Given the multiauthor, multinational composition, the editors have done a good job in producing an even and readable book. The chapters on the microanatomy and physiology of the lymphatic system, the history of lymphatic mapping, the descriptions of the basic physics of radiation and colloid particles will prove of lasting value. The background will be invaluable to those units considering setting up this type of facility and to trainees in oncological surgery. The assessments of the clinical use of procedures still in an evolutionary stage will be more ephemeral. The chapter on instructive cases is a valuable innovation and usefully portrays some of the practical problems encountered using these techniques. Overall, this book represents a useful addition to the literature on lymphatic mapping.

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Update: Surgery for the Morbidly Obese Patient

M. Deitel, G. S. M. Cowan Jr (eds)

267 × 190 mm. Pp. 539. Illustrated. 2000. Toronto: FD Communications. $195·00.

In line with the increasing prevalence of obesity and established laparascopic approaches, bariatric procedures have become quite popular. Therefore the update of Dr Deitel's book (originally published in 1989) is very timely. Aetiology, pathophysiology and comorbidities of the massively overweight are briefly mentioned. An overview of the surgical approach is followed by articles dealing with specific procedures, technical details, physiological implications and isolated complications, morbidity of fast weight loss, and benefit with respect to comorbidities, quality of life, and legal and training aspects of bariatric surgery. This work represents a real update. The interval between finishing the manuscripts and printing must have been minimal, since the authors reference articles published up to 2000. Not surprisingly, the book does not represent a unity but rather a well collected medley, trying to cover as many facets of the subject as possible. Step-by-step descriptions (e.g. endoscopy) or frequently asked questions (e.g. Swedish adjustable gastric band) underline the originality of some of the articles. So, while the book might appear a little bit unorganized, taken as a whole it is a treasure for a physician already involved in bariatric surgery, who is capable of critically dissecting the information and maybe adapting his or her own concepts. This should prevent mistakes others have already made.

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Treatment of Gallstone Patients: A Health Technology Assessment

T. Jorgensen

241 × 168 mm. Pp. 256. Illustrated. 2000. Copenhagen: Danish Institute for Health Technology.

This is an unusual book that examines the management of patients with gallstones from the perspective of health technology assessment. The text is based on a clinical epidemiological project in Denmark, and so it contains a very broad coverage of the pattern and trend of treatment of gallstone diseases in that country. The detailed epidemiological data of gallstone diseases in Denmark, including regional variations within the country, are probably of little interest to readers outside Denmark. However, the authors do provide a vigorous appraisal of the role of various technologies and the financial implications in the management of a common surgical disease; this book certainly makes a useful reference for those organizing and planning surgical services. Surgeons who are involved only in the daily management of patients with gallstones may find some of the material heavy going, but it is pleasant to read the (few) chapters on the management of the individual gallstone condition. The author has provided a comprehensive and systematic literature review of current concepts on the management of the whole spectrum of gallstone diseases, ranging from asymptomatic gallstones to complicated conditions like gallstone pancreatitis, and attempted to make recommendations on the best management strategy for each condition. These recommendations can mostly be accepted, but a few may be subjected to challenge simply because of inadequate evidence in the literature. Overall this is an excellent book on health technology assessment of gallstone management, and some of the text is also of sufficient general interest for every surgeon treating patients with gallstones to read.

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Regional Chemotherapy: Theory and Practice

D. J. Kerr, C. S. McArdle (eds)

254 × 177 mm. Pp. 107. Illustrated. 2000. Reading: Harwood Academic Publishers. £38·00.

This is a most interesting book for people who are interested in regional chemotherapy; something which is undoubtedly a Cinderella treatment. This book is a mine of information and contains a great deal of practical experience and data. It is well referenced, written by undoubted experts, and incorporates the most important areas of regional chemotherapy at the moment, including peritoneal chemotherapy, liver chemotherapy, isolated limb chemotherapy, regional chemotherapy for breast cancer and central nervous system treatments.

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Multiple Organ Failure: Pathophysiology, Prevention and Therapy

A. E. Baue, E. Faist, D. E. Fry (eds)

284 × 220 mm. Pp. 712. Illustrated. 2000. New York: Springer. £124·00.

This book is an up-to-date amalgamation of three books published in 1990 and 1991. There are 73 chapters by 116 authors who are predominantly from North America, although there are a handful of chapters from Germany and other European nations. It is extremely comprehensive with contributions from surgeons, intensive care consultants and scientists. Inevitably there is some duplication and, in common with other editions with multiple authorship, the index is a little sparse. The detail of each chapter varies. In some it is almost overwhelming and includes experimental data that await clinical confirmation. At other times there is only brief mention of everyday controversial issues. For example, I looked in vain for a comprehensive discussion about the relative benefits and risks of invasive monitoring, and about the use of intravenous albumin and other oncotic solutions. This is not a text for trainees. Within surgical disciplines the book will appeal to those who undertake major operations that are likely to provoke severe systemic upset, particularly of septic origin.

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Corrigendum

T. M. Kennedy and R. H. Jones. Epidemiology of cholecystectomy and irritable bowel syndrome in a UK population. *Br J Surg* 2000; **87:** 1658–63.

The correct version of *Table 2* is as follows:

Table 2 Prevalence of cholecystectomy in Bristol and Teesside

	Bristol		Teesside	
Age range (years)	Women	Men	Women	Men
30–39	2·40 (2·39–2·41)	NA	3·05 (3·03–3·07)	NA
40–49	5·00 (4·98–5·02)	1·70 (1·69–1·71)	2·51 (2·49–2·53)	0·93 (0·92–0·94)
50–59	7·60 (7·57–7·63)	2·10 (2·08–2·12)	6·38 (6·34–6·42)	2·20 (2·18–2·22)
60–69	5·04 (5·01–5·07)	3·60 (3·57–3·63)	10·59 (10·52–10·66)	2·75 (2·73–2·77)

Values are percentages with 95 per cent confidence intervals. NA, not available

Scientific Surgery

The *BJS* is committed to the practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on the *BJS* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Johnson CD, Kingsnorth AN, Imrie CW, McMahon MJ, Neoptolemos JP, McKay C *et al.* Double blind, randomized, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. *Gut* 2001; **48**: 62–9.
The mortality rate was similar between the groups and organ failure was evenly distributed (58 per cent placebo, 57 per cent lexipafant) in this study including 290 patients.

Lundell L, Miettinen P, Myrvold HE, Pedersen SA, Liedman B, Hatlebakk JG *et al.* Continued (5-year) follow up of a randomized clinical study comparing antireflux surgery and omeprazole in gastroesophageal reflux disease. *J Am Coll Surg* 2001; **192**: 172–9.
Some 311 patients were randomized. Surgery was more effective at controlling symptoms than omeprazole, however, increasing the dose of omeprazole in medical failures rendered the two treatments equivalent

Solomkin JS, Wilson SE, Christou NV, Rotstein OD, Dellinger P, Bennion RS *et al.* Results of a clinical trial of clinafloxacin *versus* imipenem/cilastatin for intra-abdominal infections. *Ann Surg* 2001; **233**: 79–87.
Successful outcomes were achieved in 85 per cent of patients after clinafloxacin *versus* 81 per cent after the combination (P = not significant) in this comparison involving 529 operations

Logason K, Bergqvist D on behalf of the Study Group on Antithrombotic Prophylaxis of Femorodistal Bypass Surgery. Low molecular weight heparin (enoxaparin) *versus* dextran in the prevention of early occlusion following arterial bypass surgery distal to the groin. *Eur J Vasc Endovasc Surg* 2001; **21**: 261–5.
Some 341 patients were randomized to dextran for 3 days or enoxaparin for 1 week Graft patency rates were similar (88 *versus* 83 per cent, respectively, at 3 months) but more patients who had dextran developed heart failure (13 *versus* 1 per cent)

Böhm B, Rötting N, Schwenk W, Grebe S, Mansmann U. A prospective randomized trial on heart rate variability of the surgical team during laparoscopic and conventional sigmoid resection. *Arch Surg* 2001; **136**: 305–10.
Two surgeons performed 20 operations, alternating roles as operator and assistant. Laparoscopic surgery resulted in significantly higher heart rate variability, similarly, the operator had greater heart rate variability than the assistant.

Pomier-Layrargues G, Villeneuve J-P, Deshênes M, Bui B, Perreault P, Fenyves D *et al.* Transjugular intrahepatic portosystemic shunt (TIPS) *versus* endoscopic variceal ligation in the prevention of variceal rebleeding in patients with cirrhosis: a randomized trial. *Gut* 2001; **48**: 390–6.
The study included 80 patients followed for a mean of 2 years The rebleeding rate was significantly reduced by TIPS (18 *versus* 66 per cent, P = 0 001), but the encephalopathy and mortality rates were similar.

Devine C, McCollum C on behalf of the North-west Femoropopliteal Trial Participants. Heparin-bonded dacron or polytetrafluoroethylene for femoropopliteal bypass grafting: A multicentre trial. *J Vasc Surg* 2001; **33**: 533–9.
Some 209 patients having an above knee prosthetic bypass were included 3-year patency (55 *versus* 42 per cent, P = 0 04) and need for subsequent amputation (6 *versus* 17 per cent, P = 0 015) were significantly better using heparin bonded dacron

Schortgen F, Lacherade J-C, Bruneel F, Cattaneo I, Hemery F, Lemaire F *et al.* Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomized study. *Lancet* 2001; **357**: 911–16.
Some 129 patients with severe sepsis in an intensive care unit were enrolled The use of hydroxyethylstarch for fluid replacement significantly increased the risk of acute renal failure to 42 per cent compared with 23 per cent with gelatin (P = 0·028).

Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. *N Engl J Med* 2001; **344**: 626–31.
A total of 961 patients were randomly assigned to one of three anticoagulant regimens The two low molecular weight regimens (using reviparin) increased the chance of thrombus regression from 40 to 53 per cent without increasing the risk of bleeding

Nguyen NT, Lee SL, Goldman C, Fleming N, Arango A, McFall R *et al.* Comparison of pulmonary function and postoperative pain after laparoscopic *versus* open gastric bypass: a randomized trial. *J Am Coll Surg* 2001; **192**· 469–76.
Postoperative pulmonary function was significantly better after laparoscopic surgery in this study of 70 operations In addition, the laparoscopic operation resulted in reduced postoperative pain scores and the requirement for opiate analgesia

The *BJS* website can be found at *http://www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

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Disks

IBM-compatible disks would be preferred (3½ inch). An accurate hard copy must accompany each disk, together with details of the type of computer used, software and disk system. **Do not justify.** Please send us digital versions of your figures. Ideally these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Disks will not be returned to authors.

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BJS subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; **336**: 309–15), or obtain 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2·95 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs you must state in parentheses the brief name and address of the manufacturer.** Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, patients and methods, results and discussion. Please provide a 200-word structured abstract. Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results. Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

Reviews and meta-analyses of randomized trials

The Editorial Board of the *BJS* encourages submission of review articles or meta-analyses on topics of interest. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted article will receive an honorarium. Before submission of a meta-analysis of randomized trials, authors are encouraged to consult the QUORUM statement, designed to assist in improving the quality of the submission (*Lancet* 1999, **354**: 1896–900). Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission leading articles that are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Correspondence

The Editors welcome topical correspondence. Letters should not exceed 250 words and should be typed double-spaced.

Typescripts

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This is the fourth in a series of articles on ethics, professional governance and the law.

Doctors and the law – a personal view

J. N. Johnson

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The relationship between doctors and the law used to be simple and straightforward. Once in a blue moon a clinical case would lead to litigation. It was handed over to the defence society of which the doctor was a member and was then dealt with often with little or no input from the doctor concerned. In the event of an adverse settlement a doctor's indemnity insurance paid up and life went on very much as before. I can remember cases from years ago, when, after making an initial statement to my defence society, I heard nothing further – never even discovering how the case was concluded. How times change!

First, there is the ever increasing volume of litigation and complaints, which makes preparing responses for the hospital's legal advisers a significant part of the week's work. Much is made of this increasing burden of litigation and rising number of complaints as evidence that the profession is somehow deteriorating, that consultants are uncaring and arrogant (in the media 'arrogant' is the preferred adjective to describe consultants in the way that 'botched' is the description of choice for operations) and that standards are constantly slipping. Nothing could be further from the truth. We live in a more demanding and less deferential society where consumerism is rampant, impossible expectations of health care are fuelled by governments, and patients (and consumers in general) are encouraged through Patients' Charters and similar initiatives to complain, complain and complain again. If the National Health Service (NHS) sets up a highly publicized complaints procedure permeating every aspect of the service where none existed before, there can be no surprise when the net result of this is an increase in complaints. Presumably that was the object of the exercise. It is also evident to most doctors that a system in which complaints are encouraged, even solicited, will lead to a corresponding increase in litigation. Those who argue that a good system for dealing with complaints will lead to less litigation show a devastating failure to understand human nature. Many complainants are not satisfied even when they have exhausted every avenue of the multistage NHS complaints procedure, but they will have acquired ample evidence to pursue a legal case at the end of it. In addition to this the current rules for Legal Aid in the UK make it impossible for the hospital to recover costs even if it wins, whereas the complainant suffers no financial penalty even if he or she loses. This fact alone often makes it cheaper for hospitals to settle vexatious cases rather than go to the expense of fighting them, even when the complainant has no case of substance – a fact that surgeons find extremely depressing and frustrating.

Another effect of the incessant exposure to criticism and complaints is that surgeons are constantly looking over their shoulders. This makes them far less willing to take risks for their patients even when the patient expressly wants them to do so. Many patients faced with a condition that is almost certain to prove fatal would like their surgeon to be prepared to offer them the chance of a 'risky' procedure if the alternative was likely to be an imminent demise. Hitherto this has seemed to surgeons to be a reasonable proposition, provided that the patient genuinely knows the risks involved. But now the surgeon must deal with a whole series of extraneous questions which have no bearing on the patient's well-being. 'If the patient dies, will I be criticized for undertaking a risky operation?' 'Will I be disciplined – or suspended?' 'Will it be alleged that the consent was not really informed?' 'Will it make my results for this procedure for the year look poor?'

As league tables and outcome data become more prevalent, the last question will assume a huge importance. Suppose a surgeon performs a particular high-risk procedure once a fortnight and over the previous few years has achieved a mortality rate within 30 days of operation of 4 per cent (i.e. on average one death a year). If this surgeon agrees to operate on a high-risk patient who subsequently dies, this might amount to an 'excess death' in the year in question, leading to double the mortality rate for that year. Although in statistical terms this is a nonsense, it could nevertheless be portrayed in the local media as a sudden deterioration in the standards of a particular unit. This would be particularly likely to happen if annualized league tables were made available to the press, especially if, as is often demanded, these were expressed as mortality rates *by individual surgeon*. Conversely, if a surgeon is worried about a higher than average personal mortality rate, it is the easiest thing in the world to cease to offer the operation to high-risk patients. At a stroke this will improve a surgeon's outcome figures as the factors most likely to affect outcome in high-risk adult surgery are age and co-morbidity, both of which are known before surgery is offered. No one will know that in the surgeon's mind the idea of an operation was broached and then rejected, and no blame will be attached to a surgeon who did not operate and whose patient subsequently died from natural causes. Can this trend possibly be in the patient's best interest?

But an even more frightening spectre than litigation now looms over the hapless doctor, and that is trial by media. The media does not obey the rules of evidence, does not accept that a doctor is innocent until proven guilty, even on the balance of probabilities, let alone beyond reasonable doubt. The media's guiding principle is that medical tragedies sell newspapers. Yet the effects on a doctor and his family of being plastered all over the Sunday newspapers are beyond quantification. The campaign of vilification can go on for years with tabloid papers sometimes running 'campaigns' against individual doctors or even whole hospitals. At the present time this is probably a surgeon's worst nightmare. Doctors increasingly ask not 'What is best for the patient?' or even 'How will this look in court?' but 'How will this look in the Daily —?' All of this leads to an inexorable trend towards more and more defensive medicine of the type described above.

The recent inquiry in the UK into retention of children's organs at autopsy[1] has illustrated some further medicolegal minefields that should horrify doctors who have undertaken management positions in the NHS or in universities. British surgeons, along with most hospital doctors who undertake positions in management, do so on the basis that they will continue with most if not all of their clinical work. They generally receive little if any training in management matters and are appointed on the basis that they are regarded as a safe pair of (managerial) hands by both lay managers and clinical colleagues alike. Yet the Royal Liverpool Children's Inquiry report has led to severe criticism of doctors holding management roles in the hospital and in the university at the time the events took place. The then dean of the medical school has been suspended from his current (unrelated) employment and the names of 16 doctors who held managerial positions at the time have been reported to the General Medical Council by the Department of Health. The inquiry has recommend *inter alia*: that no clinician should be appointed to a position of managerial authority in a hospital without having the relevant clinical experience for the position; that no clinician should take effective control of a management position until trained in all necessary management techniques and in any relevant legal requirements; and that no clinician should be asked to take on responsibilities that impair the ability to carry out patient care to the appropriate standard.

Given the current vogue for large clinical directorates encompassing several specialties and subspecialties, the medical manager (clinical director) will have no clinical experience of any of the specialties other than his own. He or she will almost certainly not have been trained in *all* necessary management techniques – if indeed training has occurred in any. The ability to provide patient care to the appropriate standard will be impaired, personally because management duties will restrict access to patients, and corporately because the doctor will be a party to management decisions of the hospital that may well lead to substandard patient care owing to lack of finance and other resources. If accepted, the recommendations above would bring a swift end to medical participation in hospital management. As it stands at present the Royal Liverpool Children's Inquiry has left many doctors wondering in what jeopardy they have placed themselves by offering to lend such expertise as they possess to the process of management.

In conclusion, present trends in the law as related to medicine are likely to make doctors more cautious and defensive in their approaches both to clinical medicine and to positions in management. While this will reduce the degree of jeopardy in which they are likely to place themselves, it will not always be in the interests of patients.

References

1 *The Royal Liverpool Children's Inquiry*. London: The Stationery Office, 2001.

This is the fifth in a series of articles on ethics, professional governance and the law.

Risk management

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Risk management is a new and fashionable concept in the world of healthcare. The term encompasses the reality that while risk is not avoidable it can often be reduced. The activity itself includes all types of risk to everyone within the healthcare environment, including the staff. Within a hospital the categories of risk are many, involving everything from slippery floors and inadequate fire escapes to poorly vetted locums and surgeons who 'do the odd oesophagus now and then to keep their hand in'. Although it is sometimes implied that risk management relates primarily to legal risk and is devoted to the avoidance of litigation, this is not so; it is merely a synthesis of all those activities that might reduce the risk of harm to patients and staff. There is nothing arcane about the activity, which is simply a focusing of attention on to a broader spectrum of risk than that with which clinicians are traditionally used to dealing.

No one should be under any illusion about the risks of being a patient. It has been claimed that a hospital patient has a one in 200 chance of being the victim of serious error, compared with one in 2 000 000 on an aeroplane[1]; 16·6 per cent of admissions in Australia were found to result in an 'adverse event'[2] and a Harvard study[3] found that negligent care contributed to death or permanent disability in 1 per cent of patients. A similar study recently reported in the *British Medical Journal* found even higher levels of preventable adverse events in two British hospitals[4]. Surgeons should be able to embrace the concept of risk management without difficulty, but they need to be clear where they stand in the organization when it comes to the practical business of managing risk.

Surgery is an inherently dangerous activity, and ever since the hippocratic invocation *primum non nocere* (first do no harm) the good surgeon has understood the double obligation to the patient: first, to maximize the benefit from care and, second, to minimize harm. In the pursuit of the former, the surgeon's training and competence, both clinical and technical, are carefully planned, tested and regulated, but attention to the latter, the minimization of harm, has until recently been passed over as an assumed corollary. The surgeon, one hopes, has always understood the obligation to avoid error in diagnosis, and to avoid haemorrhage and sepsis, dehydration and embolism. But the focus is now on broader issues of personal competence, team working and institutional effectiveness. Issues to be addressed include ensuring continuing professional education, not operating outside one's field or beyond one's competence, and checking that trainees are properly assessed and supervised, that medical records are full, accurate and legible, and that handovers are effective in ensuring safe continuous care. These, you might think, are straightforward professional obligations, but the objective of clinical risk management is ensuring that the process of care avoids the hazards to the patient that persist even when the surgeon's clinical and operative skills are impeccable.

What distinguishes these new obligations from the traditional is that they are so often to do with ensuring that clinicians and the institution together work optimally for the patient. This needs to be a *formal* process, not just part of an informal professional ethos. The difficulty inherent in such a formal process is that it extends the surgeon's responsibilities to areas outside his or her immediate control into areas that overlap with those of managers and planners. Surgeons, none the less, usually feel few inhibitions about advising managers how best the organization might be run so as to reduce risk, how to define adequate staffing levels and a physically appropriate environment, and how to implement processes that would enable staff to do their job in an unhurried, considerate and safe way. Yet many surgeons still have difficulty when outsiders return their interest by identifying issues within the surgeon's immediate sphere of influence where there is risk to be reduced: poor attention to hand washing, sloppy arrangements for consent, poor communication, a preference for treatment for which there is no evidence of benefit, and so on. Clinicians' resistance to outside intrusion is so familiar that clinical risk is increasingly being managed by the defining, imposing and policing of rigid protocols for the management of patients, and by proselytizing clinical governance.

It is easy to make a strong case for pressing on with this sort of risk management and, conceptually at least, it is sound. However, there is a downside. Risk management activities offer an opening for the unhealthy bureaucratic and regulatory instincts of some people. Protocols rely too heavily on explicit rather than tacit knowledge[5], and may reflect just one set of clinical options when others may be equally valid. Their heavy-handed imposition may stifle innovation, deny the responsibility inherent in professionalism, and be time consuming, expensive and demoralizing. Risk management programmes that actively search out adverse incidents, unless handled very sensitively, may simply be seen as an extension of the currently prevalent culture of blame and thus be counterproductive.

Risk management is an extension of our normal clinical responsibilities; the activity, if not the buzzword, is here to stay and it requires a cultural change for us all. Surgeons inside looking out need to understand that, in the interests of safety, every nook and cranny of their business can quite properly be inspected and commented on. Those on the outside looking in need to be more aware of the harm they can do. They must trust professionals more, and be prepared to have their own interventions assessed and, if necessary, repudiated on grounds of effectiveness and value for money. A scrutiny of the scrutineers is all too often lacking.

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The Editors

Review

Clinical and economic evaluation of surgical treatments for faecal incontinence

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Background: Faecal incontinence affects 1–2 per cent of the adult population. While many patients can be managed successfully with conservative therapy, a small proportion require surgery. Improved imaging techniques and technological advances have led to the availability of a wide range of surgical treatments. Decision-makers increasingly require clinical and cost-effectiveness studies of surgical treatments for faecal incontinence. This review examines the practical aspects of undertaking such studies.

Methods: The practical issues related to different aetiologies, different types of treatment, defining outcomes, the hidden costs of the condition and its treatment, the rapid changes in technology and issues of patient choice were all considered. A Medline search was undertaken to identify relevant publications, and the reference lists of identified papers were scanned manually.

Results: There are few randomized controlled studies and those that have been performed have been limited in their scope. There has also been very limited health economic analysis undertaken. Strategies for conducting such studies, and the criteria they use, have been outlined.

Conclusion: Randomized trials have a limited role in this setting because of variations in aetiology, difficulty in standardizing procedures, continuing evolution of devices, small patient numbers, concerns for patient choice and the need for long-term follow-up. Issues to be addressed when evaluating interventions for faecal incontinence include choosing appropriate measures of surgical outcome, using new continence scoring systems and tools for quality-of-life assessment, and choosing appropriate cost perspectives and time horizons for economic evaluation.

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Introduction

Faecal incontinence is more prevalent than previously thought. Early studies may have underestimated the true prevalence as a result of the social stigma attached to declaring its presence and seeking treatment[1]. Incontinence to stool or flatus occurs weekly or more often in 2·2 per cent of adults[2]. There is a higher rate of faecal incontinence in women, with obstetric-related structural sphincter damage a common aetiological factor[3,4]. Prevalence rises with age[5], reflecting degenerative changes of the sphincter mechanism with time[6–8]. Incontinence has been reported in 7 per cent of otherwise healthy adults over age 65 years[9]. Recent reports on the prevalence of incontinence may reflect not only a greater public and medical awareness of the condition itself, but also its heightened profile among clinicians following the introduction of advanced diagnostic modalities such as anal endosonography[10] and endocoil anal magnetic resonance imaging[11]. These have led to increased rates of identification of surgically correctable causes of incontinence, and to increased referral rates for definitive treatment to tertiary centres with a specialist interest in this area.

Faecal incontinence can be either passive or urgent in nature. Passive incontinence relates to losses occurring without patient awareness, usually in association with internal sphincter dysfunction and reduced maximum resting anal pressure. Patients with urge incontinence are unable to defer defaecation until a socially acceptable time, which usually reflects either external sphincter dysfunction and reduced maximum voluntary contraction, or excessively strong bowel contraction that cannot be opposed by the external sphincter pressure[12]. The adverse consequences of faecal incontinence on patients' well-being and social role fulfilment may be substantial. Embarrassment, stigmatization, loss of self-esteem, difficulty travelling and maintaining employment, and strain on interpersonal relationships frequently result in social isolation, depression and a generally reduced quality of life. The economic implications of faecal incontinence are also substantial, impacting on individual patients and other family members, as well as healthcare providers in acute and primary care settings. Resources used in the hospital sector include those of investigation and diagnosis, exclusion of other pathologies, and specific treatments and follow-up offered to individual patients. Resources used by patients include drug treatments, stoma products, incontinence pads, sanitary products and increased laundry needs. In addition, patients may require frequent consultation with family doctors, stoma care nurses and other community healthcare workers, and may incur substantial travel costs in seeking care. The wider impact on society includes the premature need for nursing home placement and the inability of patients to engage in full employment or home-working tasks.

Many patients can be managed by means of pharmaceutical products, such as loperamide or codeine phosphate[13,14], and/or behavioural interventions, such as biofeedback training[15]. The overall proportion of incontinent patients who ultimately have an operation is unknown. Of those who do have surgery, the majority have problems that are correctable by less invasive procedures, such as overlapping external sphincter repair. Some patients, with more extensive structural damage or congenital anorectal anomalies, need a more major reconstruction or colostomy formation. Hospital stays for those receiving definitive surgical treatments can be lengthy; the procedures themselves require considerable operating time and some procedures, such as dynamic graciloplasty[16] and artificial anal sphincter implantation[17], may require a sequence of hospital admissions and detailed follow-up.

Incontinence is one of the commonest reasons for nursing home placement[18]. Over a decade ago it was estimated that more than US$400 million was spent annually in the USA on faecal incontinence appliances[18]. However, detailed estimates of resource usage and associated costs of faecal incontinence are limited. A Canadian study[19] estimated that the annual cost per patient of managing incontinence in institutionalized patients was nearly Can$10 000.

A recent American study reported the monetary costs of evaluation, treatment and projected follow-up of 63 women with obstetric-related faecal incontinence[4]. The average cost per patient was US$17 200, 52 per cent of which was for surgical treatments (received by 59 per cent of the women). Evaluation and follow-up costs were low, comprising less than 10 per cent of total costs, with physiological assessment accounting for two-thirds of these. The cost of protective materials for those failing treatment was substantial. This study highlights the difficulties in estimating the cost of care for these types of patient. The authors indicated that their results were likely to be underestimates, as they did not include the cost of primary sphincter repair at the time of delivery, anaesthetic cost for all surgical procedures, cost of evaluation and follow-up performed elsewhere, and indirect costs such as time off work. In projecting estimates forward over a lifetime it was assumed that symptoms would remain at the same level, which may also underestimate the longer-term costs as severity and prevalence of incontinence are likely to increase with age, perhaps leading to institutional care for some patients[5]. Costs derived from patient recall of resource use may be inaccurate, and charges provided by billing databases may exceed true economic costs. Nevertheless the analysis included adjustments for inflation and consideration of discounted service fees agreed between insurance companies and health organizations. The authors also allowed for a 'grace period' following surgery during which surgical consultations are not billed separately in the USA. Finally, and importantly, they noted that, despite the costs incurred over the period of the study, many patients had ongoing symptoms of faecal incontinence at follow-up, suggesting that concentration on cost alone in such analyses may be inadequate.

In recent years an improved understanding of the pathophysiology of incontinence has led to the rapid development of newer surgical treatments and devices. Traditional operative approaches of overlapping sphincter repair, postanal repair and colostomy have now been supplemented by others, such as dynamic graciloplasty[16,20–22], artificial anal sphincter implantation[17,23,24], sacral nerve stimulation[25–27], injection sphincter augmentation[28], conventional and dynamic gluteoplasty[29], antegrade continence enema procedures[30,31] and colonic conduit formation[32]. Each of these operations may involve substantial early use of health service resources, but has the potential for longer-term savings and increased quality of life in selected patients.

The different surgical interventions used to treat faecal incontinence vary widely in cost. The simpler operation of overlapping sphincter repair for patients with a discrete external sphincter defect, usually obstetric or postsurgical, is inexpensive and associated with 70–80 per cent continence to stool at short-term follow-up[33]. Although continence after surgery deteriorates with time, about half the patients receive long-term benefit from surgery[34]. Postanal repair is also a straightforward procedure with relatively low in-patient care costs, although giving lower long-term success rates[35]. Diverting stomas have moderate costs associated with the initial operation, but considerable ongoing costs of stoma appliances and management of stoma-related complications, such as parastomal herniation, obstruction and stomal prolapse. Procedures requiring an implanted device, such as insertion of the artificial anal sphincter, dynamic graciloplasty and sacral nerve stimulation, have high initial costs associated with prostheses and technical equipment, in addition to operating and in-hospital costs. The devices themselves also require periodic scheduled or unscheduled replacement. High complication and reoperation rates following more complex reconstruction procedures, such as dynamic graciloplasty[21,36], artificial sphincter implantation[24], antegrade continence enema procedures[30,31] and colonic conduit formation[32], raise costs further. Staging of procedures, for example with a covering stoma or gracilis devascularization, also impact heavily on costs and clinical outcomes. Associated with the development of newer surgical procedures there is often a learning curve[22,37,38], resulting in improved outcomes and perhaps lower intervention costs for later cohorts of patients. Patients are rarely fully continent after any type of surgery, and the ongoing costs associated with treatment of residual symptoms may be considerable.

Reported studies of surgical management of incontinence frequently contain limited data on often poorly defined clinical outcomes. Few studies have attempted to assess long-term outcomes in relatively homogeneous and well defined patient groups. Most assessments include patients with varied aetiology[36,39] and do not use standardized techniques of investigation, surgery or evaluation. There are ethical and practical problems of performing randomized controlled trials of surgical interventions in these groups of patients. The few such trials that have been reported have included small numbers of patients and have had relatively short periods of follow-up (*Table 1*). For this reason the evidence on the efficacy of individual treatments is not strong and clinical effectiveness over the long term has rarely, if ever, been established.

It is the responsibility of policy-makers and healthcare purchasers to assess whether society can, or should, invest in a new intervention; they must compare it with other potentially attractive calls on their constrained budgets. They increasingly require evidence not only of clinical effectiveness, but also of cost-effectiveness, before authorizing the use of new technologies in healthcare. Pharmaceutical companies are becoming familiar with some form of 'fourth hurdle' in which information on the cost-effectiveness of their products needs to be presented and appraised before reimbursement may be approved by national or local authorities[44–48]. The National Institute of Clinical Excellence (NICE) in the UK and parallel initiatives elsewhere represent a broadening of this approach to devices and surgical procedures. The current work programme for NICE includes five devices, five procedures and 12 drug therapies. The growth of government-sponsored health technology assessment raises issues of defining and collecting appropriate information on new surgical procedures and device technologies to enable them to be fully assessed and officially approved for use and reimbursement by the healthcare system.

Surgical interventions, often resource intensive in the short term, may result in considerable health benefits and

Table 1 Randomized trials of surgery for faecal incontinence

Reference	Year	Treatments compared	No. of patients	Follow-up (months)	Primary outcome measures
Deen *et al.*[40]	1993	Anterior levatorplasty *versus*	12	24 (median)	Failure to achieve full continence
		Postanal repair *versus*	12		No change in incontinence
		Total pelvic floor repair	12		
Deen *et al.*[41]	1995	Total pelvic floor repair *versus*	18	16·1 (mean)	Faecal incontinence scores
		Total pelvic floor repair + IAS plication	15		
van Tets and Kuijpers[42]	1998	Total pelvic floor repair *versus*	11	41 (mean)	Failure to achieve full continence
		Postanal repair	9		No change in incontinence
Yoshioka *et al.*[43]	1998	Total pelvic floor repair *versus*	12	18 (mean)	Faecal incontinence scores
		Gluteus maximus transposition (without electrical stimulation)	12		

No significant differences were found in any of the trials. IAS, internal anal sphincter resource savings in the medium to long term. The remainder of this review outlines the key principles of economic evaluation and the issues raised in obtaining appropriate information specifically for surgical treatments for faecal incontinence.

Economic evaluation of surgical procedures for faecal incontinence

There is limited information available on the cost-effectiveness of surgery for faecal incontinence. Adang *et al.*[49] compared the costs and outcomes of dynamic graciloplasty with conventional medical treatment (diaper/enema) and colostomy/stoma care in patients with faecal incontinence in the Netherlands. The lifetime direct costs of each option were estimated to be Dfl56 000 (approximately £16 700) for graciloplasty, Dfl21 300 (£6400) for medical care and Dfl125 000 (£37 400) for colostomy and stoma care. Quality of life was improved for patients treated by graciloplasty. Compared with colostomy and stoma care, the initial high cost of graciloplasty was outweighed by the savings in ostomy supplies within 5 years, assuming a device life of 5 years or more. Unfortunately, the groups used in this study were small. Stoma care costs were based on only seven patients, with somewhat higher estimated costs than those expected in the USA[50]. In addition, the data were not analysed on an 'intention to treat' basis. In such evaluations it is important to include the costs of surgical failure, which may involve successive revisions, and of physiological testing and counselling for patients who do not eventually undergo operation. The study did not link costs with effectiveness directly.

The randomized controlled trial paradigm of clinical assessment developed for pharmaceuticals, and adopted by advocates of health technology assessment and government bodies such as NICE, is problematic when applied to surgical interventions and medical devices. The development of devices is generally rapid, and subject to continuous and iterative dialogue between the manufacturer and the surgeon or other user of the device. Surgical procedures may not be standardized, either within a single institution or between different centres, and skill levels may vary between individual surgeons. Techniques are likely to improve over time as the surgical team progresses up the learning curve. Hence any evaluation is aimed at a moving target; by the time a trial has been completed, a technique or device may have improved, rendering the results of the exercise obsolete[51]. Typically, devices have a limited number of potential end-users (and therefore potential trial participants) and obtaining informed consent for invasive procedures can be difficult. It may be hard to distinguish the relative contribution of surgical skill, device design, drug therapy and changes with follow-up on the health outcome. The device industry consists of relatively small firms supplying niche markets, with limited capacity for undertaking major trials[52]. In conclusion, the methods used to evaluate the benefits of a device or surgical procedure must of necessity differ from those applied to drug development.

Methodological issues in the evaluation of surgical procedures for faecal incontinence

Study design

Comparison of different treatment strategies requires some standardization of both study design and of the endpoints and outcomes used to assess the clinical result. There are ethical and practical problems in using randomized controlled trials to compare surgical and medical treatment modalities for faecal incontinence. First, incontinence is highly variable in aetiology, type (urge, passive or both), clinical severity and effect on individual patients. Those suitable for some surgical treatments may not be suitable for others. For example, women with sphincter disruption following childbirth who fail non-surgical management may be treatable by overlapping repair, dynamic graciloplasty, artificial anal sphincter insertion or colostomy. Clearly it is more appropriate to attempt the simpler and less disfiguring overlapping repair in the first instance. A randomized trial placing patients into one of these four potential treatment arms would be unethical, as it would unreasonably expose patients to the more serious and frequent complications of the more complex procedures, or to the body image problems associated with a stoma.

Probably the closest target populations in terms of suitability for candidate procedures are those formed by patients in whom the alternatives of dynamic graciloplasty and implantation of an artificial anal sphincter are considered appropriate. A randomized trial comparing even these two procedures would place the two groups of patients at risk of two entirely different sets of complications of differing reported incidence: the graciloplasty group to a high morbidity and reoperation rate (up to 50 per cent) and a high electrical device failure rate[21,36], and the artificial sphincter group to a significant, but probably lower, morbidity rate, related mostly to implant sepsis and functional device failure[24]. There is no accepted single standard surgical procedure (or other patient management) for patients with each particular aetiology and degree of incontinence, and so none that can be used for comparison with any new procedure under evaluation. Placebo treatment may be unethical for these patients. Given these fundamental differences between the two treatments, informed consent would be difficult to achieve for any randomized comparison. Given this inability to perform randomized controlled trials, direct comparison must be based on prospective observational studies. However, even these are constrained by an inability to match cohorts closely owing to patients choosing different options. Some adjustments must be made for differences in baseline characteristics.

Continence scoring systems

It is important to standardize the assessment of incontinence by using formal scoring systems. This enables a comparison of continence in the same patient at different times, of groups of patients in different centres, and of treatments. The Cleveland Clinic[53] and St Mark's Hospital[54] continence scoring systems are improvements over previous systems, by including in one global assessment not only continence to stool and flatus, but also the frequency of losses, the need to use pads and the effect of incontinence on lifestyle. The latter system also incorporates the ability to defer defaecation for over 15 min and the use of constipating medications.

Probably the greatest drawback of all the currently available scoring systems is their inability to assess passive incontinence in any detail. Passive incontinence, unlike urge incontinence, is uncommonly a single event but rather an ongoing leakage over time. By definition it is not usually noted until some time after the leakage, and hence the assessment of frequency and the volume of losses are difficult to quantify. A further weakness is that the same continence scores may be obtained by very different combinations of factors in different patients, which may not represent similar clinical expressions and levels of incontinence.

When comparing a stoma against other surgical therapies, continence in itself is an inadequate endpoint for assessing surgical success, and continence scores are irrelevant. Although patients with a stoma may be technically continent *per anum*, many suffer from difficulty of body image. Many also experience lesser degrees of ongoing passive anal incontinence from the retained rectal stump. None of these issues has yet been incorporated into any continence scoring system. While good scoring systems are now available and should be used, their limitations must be recognized when dealing with passive incontinence or when assessing the benefit of a stoma.

Measurement of health outcome

A major difficulty in assessing clinical and cost-effectiveness of surgery for incontinence lies in finding an appropriate measure of health outcome. Degree of continence to solid and liquid stool in itself does not necessarily reflect or directly correlate with the social consequences of incontinence. Outcome measures of relevance to health technology assessment include both objectively measurable clinical outcomes (continence) as well as patients' own assessment of the intervention's impact on lifestyle, such as the ability to travel, maintain employment and the effects on interpersonal relationships. A patient reporting no urge incontinence after operation may achieve this result by remaining housebound to permit immediate access to a toilet when faecal urgency occurs. Although technically continent, this lifestyle restriction is substantial and the result cannot be considered simply as surgical 'success'. On the other hand, many patients who are not rendered fully continent (surgical 'failures') may be sufficiently improved by operation for there to be a significant improvement in their quality of life, and to result in good patient satisfaction[34]. The relationship between symptom improvement and quality of life may not be linear or even continuous; a relatively small reduction in symptoms may be enough to enable a return to work or social activities, with a substantial improvement in quality of life. Intervention may have a threshold relationship with quality of life.

There are many generic, well validated quality-of-life instruments available, but there is only one validated instrument specific to faecal incontinence[55]. It comprises four scales: lifestyle, coping/behaviour, depression/self perception, and embarrassment. Experience with this new instrument is as yet small. Quality-of-life instruments that give multidimensional health profiles are of limited worth for economic evaluations, which require single measures of health outcome in order to derive cost-effectiveness ratios. Recent efforts to develop such measures have led to short purpose-built generic instruments such as the EuroQol 5D[56] or the Health Utilities Index[57]. These are based on patients' preferences for the level and mix of health outcomes. In summary, health outcome assessment should utilize both disease-specific and generic quality-of-life instruments. Information for economic evaluation requires the use of specific generic instruments.

Time horizon

An appropriate time horizon needs to be chosen for economic evaluations. The potential increase in quality of life and cost savings, for example by avoiding the need for stoma care, resulting from the new intervention may persist for many decades. Implanted devices will have failure and replacement rates, and repeat operations may be necessary. The economic evaluator is not at liberty to wait for the maturing of data on the long-term follow-up of these patients. In this situation it is appropriate to use a modelling approach, in which existing data on quality of life, resource use, device failure and replacement rates, and patient survival can be projected forward using explicit assumptions[58]. Distinction must be made between the cost and short-term health impact of initial acute care, subsequent operative or device failures, and the long-term 'steady state' health outcomes and quality of life of patients after the initial intervention. The assumptions involved in projecting experience over patients' anticipated lifetimes are tenuous. It is therefore advisable to use an intermediate time horizon of 5 or 10 years for an economic evaluation.

The cost perspective

Economic evaluations have meaning only if the context is defined. The broad 'societal' cost perspective favoured by economists includes not only the immediate and long-term health and social care costs, but also personal, travel and indirect costs. Indirect costs refer to economic productivity at work or at home, although there is debate about how these should be valued[59,60]. Estimates of changes in indirect costs and social care costs resulting from interventions for patients with faecal incontinence are likely to be based on very few cases and will therefore lack precision. Inclusion of indirect costs may tend to favour patient groups of working age. The most compelling health economic arguments are based on direct costs of health and social care. Indirect costs should be considered separately.

Practical issues

There are major practical issues to be faced when applying evaluations in this field. They stem from the relatively small patient numbers being treated at widely dispersed centres in different countries. Country- and site-specific patterns of acute care (surgery) and long-term care present problems for the ascertainment, pooling and valuation of resource use across study centres. The translation and validation of new instruments is lengthy and expensive. The generalizability of economic results to different settings or countries may be compromised by using specialist centres with highly selected patients for the evaluation.

Conclusion

Faecal incontinence is a common and distressing physical disability that makes major demands on healthcare resources. At a time of increasing pressure on health budgets, there is a growing requirement to demonstrate the clinical effectiveness and cost-effectiveness of new treatment options in order to make the best use of resources. Currently, few clinical and economic evaluations of treatment options for faecal incontinence exist; randomized controlled comparisons present formidable ethical and practical problems. Comprehensive evaluation requires a clearly defined perspective, a sufficiently long time horizon, appropriate measures of health outcome, assessment of quality of life, and detailed measures of short-term and projected resource utilization. Although unfamiliar to many clinicians, these complex issues require increasing attention by those wishing to demonstrate the true value of new interventions for faecal incontinence.

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Review

Anorectal injury following pelvic radiotherapy

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Background: Current knowledge of the effects of radiation on the anorectum is based on a limited number of studies. Variability in delivery techniques, both currently and historically, combined with a paucity of prospective and randomized studies makes interpretation of the literature difficult. This review presents the existing evidence and identifies areas that require further work.

Methods: This review is based on a literature search (Medline and PubMed) and manual cross-referencing.

Results and conclusion: More than three-quarters of patients receiving pelvic radiotherapy experience acute anorectal symptoms and up to one-fifth suffer from late-phase radiation proctitis. About 5 per cent develop other chronic complications, such as fistula, stricture and disabling faecal incontinence. The risk of rectal cancer may be increased. Conservative treatment options are of limited value. Surgery may be considered if symptoms are severe, provided sphincter function is adequate and recurrent disease is excluded. Large prospective studies with accurate dosimetric data and long-term follow-up are needed to provide meaningful information on which to base new strategies to minimize the side-effects from radiotherapy.

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Introduction

The use of radiation as a medical therapy is a relatively recent phenomenon. Experimental studies of the biological effects of radiation were started in 1898 when Pierre Curie used a radium tube to produce an ulcer on his arm, and charted its progress and ultimate healing[1]. Modern external-beam radiotherapy was born in the 1950s with the development of mega-voltage linear accelerators. Radiation therapy now has a major role in the treatment of a number of malignancies arising in the pelvis. Carcinoma of the prostate, bladder and rectum, and gynaecological malignancies, are commonly treated with external-beam radiotherapy, sometimes with the addition of brachytherapy (local delivery of radiotherapy)[2]. Rectal injury after pelvic radiotherapy is well documented[3], but anal canal injury and anorectal dysfunction receive scant attention in the literature.

This article presents current understanding of the clinicopathological and functional effects of radiotherapy on the anorectum, and discusses the various therapeutic options that are available. A limited background on the mechanisms of radiation injury and some general points about radiotherapy delivery are included for the benefit of general surgical readers.

Methodology

An electronic search for relevant articles in English over the last 50 years was undertaken using the Medline database via PubMed. The terms pelvic radiotherapy, radiation injury, rectum and anus were searched as text items. The corresponding Medline Subject Heading (MESH) terms (radiotherapy, radiation injuries, rectum, anus) were also searched. Manual cross-referencing of the retrieved papers was undertaken. Based on these methods, references considered of interest or thought to contain well validated new information were included.

Mechanisms of injury and radiation delivery

Ionizing radiation affects the process of cell division and depopulates a tumour of its malignant cells, mainly via direct effects during mitosis. High-energy X-rays collide with body tissues, resulting in ionization and the release of high-energy electrons and free radicals that damage cellular DNA. The damage caused prevents normal mitosis from occurring, resulting in cell death during attempted division. Despite DNA damage, most cells continue to carry out their other normal physiological functions until mitosis occurs[4,5].

In the clinical setting, radiation is usually given in 'fractions' of the total treatment dose over several weeks. This fractionation has a number of advantages. It allows rapidly proliferating normal tissues to repopulate and slowly proliferating normal tissues to repair DNA damage more effectively than tumour cells[6]. Fractionation also allows more tumour cells to move out of the relatively protected S phase of the cell cycle, making them vulnerable to radiation. Finally, revascularization of hypoxic areas in a tumour mass between fractions results in their reoxygenation[7], enhancing their radiosensitivity.

External-beam radiotherapy is usually delivered to the pelvis using a three-field technique, typically with an anterior and two lateral beams. This provides the maximum dose to the area to be treated while allowing minimal doses to adjacent radiosensitive areas, such as the rectum and femoral heads[8]. Although it is beyond the remit of this review to detail specific treatment regimens, some examples of total treatment doses and fractionation regimens are shown in *Table 1*. Total-body computed tomography (CT) requires a dose of about 0·01 Gy. Abortion would be considered if a fetus received a radiation dose greater than 0·2 Gy. The rectal tolerance dose (TD$^{5/5}$), defined as the dose expected to result in a serious rectal complication in 5 per cent of patients within 5 years, is 45–50 Gy.

Pathological features

Rectum

Owing to its fixed position in the pelvis, the rectum is the commonest site of bowel injury after pelvic radiotherapy[9–13]. Early inflammation is described as acute-phase radiation proctitis. Late-phase radiation proctitis occurs from 3 months after treatment. Proctitis is dependent on the dose of radiation[11] and the rectal volume in the irradiated field[14]. Factors such as diabetes and combination with chemotherapy have been shown to increase the incidence of proctitis[15,16].

The microscopic features of acute-phase proctitis include meganucleosis, fibroblastic proliferation, inflammation of the lamina propria, eosinophilic infiltration, lack of mitotic activity and loss of crypts[17,18]. There is mucosal hyperaemia, which may be accompanied by excessive production of mucus. With increased doses a pellicle of dead cells forms on the mucosal surface, and this may separate before the epithelial and submucosal layers have regenerated, leaving an ulcerated area. When complete epithelial loss occurs it is replaced with fibrous tissue, resulting in a scar.

The microscopic appearances in late-phase radiation proctitis include severe vascular changes, with narrowing of arterioles by subintimal fibrosis, telangiectasia of capillaries and postcapillary venules, endothelial degeneration and platelet thrombus formation. These vascular changes are associated with fibrosis of the lamina propria and crypt distortion[19]. After chronic radiation exposure, fibrosis of supporting tissues results in contraction and stricture formation, and the decreased regenerative properties of damaged tissue may result in fistula formation. Other features of chronic radiation injury include histological changes in the smooth muscle and neuronal plexuses in the gut wall. Varma *et al.*[18] described hypertrophy of the muscularis mucosae and the muscularis propria. Neuronal hypertrophy was seen in the muscular (Auerbach) plexus but not in the submucosal (Meissner) plexus. A decreased number of ganglion cells with vacuolation and degranulation also provides evidence of significant insult to the myenteric nerves.

Anal canal

Despite an extensive search of the literature, histological reports of changes in the anal canal after radiotherapy were

Table 1 Typical radical treatment doses for pelvic malignancy

	Total dose (approx.)	Fractionation regimen	Notes and alternatives
Prostate	64 Gy	32 fractions in 6·5 weeks	Dose escalation with 3D-CRT and IMRT; iodine–palladium seeds; high dose rate brachytherapy
Bladder	64 Gy	32 fractions in 6·5 weeks	
Cervix	45 Gy (plus 15 Gy brachytherapy)	25 fractions in 4 weeks	2 × 7·5 Gy additional brachytherapy (e.g. high dose rate iridium)
Rectum	20 or 50 Gy	Five fractions in 1 week 25 fractions in 5 weeks	Immediately before operation 3–5 weeks before operation

3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy lacking. Short- and long-term effects on sphincter morphology are unknown.

Clinical features

Rectum

Up to 75 per cent of patients undergoing pelvic radiotherapy[20,21] will experience some rectal symptoms during the treatment period[13], some so severe as to interrupt treatment[22]. Symptoms include rectal bleeding, rectal pain, diarrhoea, tenesmus, faecal frequency and faecal urgency. Bleeding occurs as a result of mucosal friability and neovascular telangiectasia[23]. Proctitis can be scored with regard to symptoms, endoscopic appearance and histological findings. A scoring system such as that described by Talley *et al.*[24] (*Table 2*) is a helpful objective measurement in the assessment of proctitis.

Long-term sequelae

The peak incidence of late complications, such as rectal stricture or fistula formation, occurs between 2 and 5 years after radiotherapy[25], although late presentation has been reported up to 30 years after treatment[26]. Heavily irradiated tissue has vastly reduced regenerative properties. Even relatively trivial traumatic or infective insults can result in severe tissue breakdown, leading to problems when operating in an irradiated field[27]. Pelvic irradiation may cause persistent diarrhoea by affecting not only anorectal function but also gut transit and intestinal absorption of fat, bile acids and vitamins[28].

The incidence of late radiation-induced injury depends on the nature of the radiation injury and patient factors. In 738 patients treated with external-beam radiotherapy for prostate cancer[25] there was an 8 per cent 10-year cumulative incidence of moderate proctitis, enteritis and anorectal stricture, and a 3 per cent incidence of severe proctitis, small bowel obstruction and fistula formation. Sixty-one (4·3 per cent) of 1418 patients treated with radiation for carcinoma of the uterus developed significant radiation-induced complications requiring surgical referral[29]. Advances in radiotherapy treatment planning and the use of newer techniques, such as three-dimensional conformal radiation therapy and intensity-modulated radiation therapy, may reduce complications by allowing dose distributions that conform closely to the three-dimensional shape of the target volume while minimizing the dose to adjacent structures[30].

In the longer term an increased incidence of rectal cancer has been reported following pelvic radiotherapy[31]. MacMahon and Rowe[32] suggest that early and late radiation proctitis, rectal stenosis and induration of the rectovaginal septum may be risk factors for the development of secondary cancer. However, rectal cancer may develop in the absence of clinical proctitis. In Jao *et al.*'s large series of 76 patients with radiation-induced colorectal cancer[33], 85 per cent had histological evidence of a radiation reaction around the cancer but only 17 per cent had symptoms of proctitis. The relationship between radiation dose and risk is not clear. In a study of rat colons[34] irradiated with a range of doses from 25 to 65 Gy, the dose producing the maximum number of tumours was 45 Gy. Although there are no cohort studies to support rectal surveillance for

Table 2 Scoring system for symptoms, and endoscopic and histological results[24]

	Score		
	0	1	2
Symptom			
Urgency	None	Mild (5–20 min)	Moderate or severe (< 5 min)
Bleeding *per rectum* (per week)	0	< 4	≥ 4
Quantity of blood per rectum	None	Streaks	Obvious
Diarrhoea (days per week)	0	1	> 1
No. of stools	≤1	2–3	> 3
Rectal pain	None	Pain present	—
Endoscopy (rectum)			
Erythema	None	Mild	Moderate
Granularity or oedema	None	Mild	Moderate
Telangectasia	None	Few or some	Sparse or florid
Ulcer	None	Few or numerous	—
Histology			
Overall grade	Normal	Abnormal	—

cancer, this has been recommended beginning 5 years after pelvic radiotherapy[35].

Anal canal

Anal discomfort may occur in the acute phase after radiotherapy and may be compounded by radiation-associated diarrhoea. The dose received by the anal canal depends on its proximity to the target volume. Injury to the anal sphincter complex after pelvic radiotherapy has been reported, although evidence is indirect and based mainly on observed functional disturbances[18].

Anorectal injury and incontinence

Continence is dependent on stool consistency, bowel activity, sphincter function[36] and rectal capacity[37]. Pelvic radiotherapy may affect these factors; the reported incidence of faecal incontinence following pelvic radiotherapy ranges from 0 to 26 per cent[38,39]. The wide variation may be explained by differences in target site, patient mix, delivery techniques, doses received and how rigorously symptoms were sought.

The reported rate of incontinence following external-beam radiotherapy for anal carcinoma varies widely, from 0 to 57 per cent[40–48], with an average incidence of about 25 per cent. These patients receive 45–60 Gy directly to the anus, a greater anal dose than that received in any of the pelvic radiotherapy regimens discussed above. If direct sphincter injury was the main cause of incontinence following radiotherapy, it would be reasonable to expect a higher incidence of incontinence in this group. Broens *et al.*[49] proposed that damage also occurs to the anal epithelium and haemorrhoidal cushions. This may be a further mechanism contributing to anal dysfunction as these structures constitute an important component in maintaining anal closure.

Investigations

Rectum

Sigmoidoscopy

The classical appearances of radiation proctitis, directly visualized via a rigid or flexible sigmoidoscope, are pallor or erythema, prominent telangiectasia, mucosal friability and ulceration[17]. Sigmoidoscopy has the advantage of allowing tissue diagnosis, although fibrosis, luminal narrowing and rigidity of the rectal wall may impede advancement of the instrument, preventing examination of the entire abnormal area[50].

Barium enema

The main radiological features of radiation injury are decreased distensibility of the bowel wall, intestinal fixation, stenosis and fistula formation. If stenosis is present, a lack of prestenotic dilatation is characteristic. Barium enema is less sensitive than endoscopy in outlining mucosal abnormalities and ulceration, but is reliable in showing the extent of disease[50].

Transrectal ultrasonography

Transrectal ultrasonography (TRUS) has been employed in the assessment of chronic rectal complications after pelvic radiotherapy for carcinoma of the cervix. In 67 patients the most consistent finding was thickening of the perirectal connective tissue associated with obscuring of the echogenic submucosal layer in the anterior rectal wall[51]. TRUS has been used to detect recurrent prostate and bowel cancer but there are no reports on its reliability in differentiating malignant change from radiation change.

Computed tomography

The commonly described features of radiation injury on CT are increased density and thickening of the perirectal fat, thickening of the perirectal fascia and rectal wall, and fibrosis between the sacrum and rectum[52]. However, the sensitivity of CT in differentiating radiation change from recurrent or secondary malignancy is debatable[52,53].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) shows increased signal intensity with the inflammatory changes associated with pelvic radiotherapy, and these increase significantly with radiation dose[54]. Irradiated soft tissues also show enhancement with intravenous gadolinium contrast agent[55]. A characteristic pattern of varying oedema after radiation has also been described[56]. MRI may be reliable in differentiating radiation change from recurrent tumour in cases of carcinoma of the vagina and cervix[57,58], but appears less reliable in rectal cancer[59].

Positron emission tomography

Positron emission tomography (PET) has been investigated as a tool for distinguishing tissue change associated with radiotherapy from tumour recurrence. Owing to the enhanced glycolytic activity of proliferating cells after radiation injury, it has not been possible to distinguish between proliferation, repair, inflammation and residual viable tumour cells. PET may prove more useful in detecting recurrence from 6 months after radiotherapy, by which time much of the inflammatory reaction has resolved[60].

Anal canal

Anorectal physiological testing

The results of anorectal physiological studies after pelvic radiotherapy have been inconsistent (*Table 3*)[18,39,61–66].

Table 3 Effects of radiation on anorectal physiology

Reference	Radiation dose (Gy)	Target organ	Maximum anal canal resting pressure	Squeeze increment	Rectal threshold volume	Maximum tolerated rectal volume
Varma *et al.*[18,61]	50	Prostate	Decreased	No change	—	Decreased
Birnbaum *et al.*[62]	45	Rectum	No change	No change	—	—
Birnbaum *et al.*[63]	45	Rectum	No change	No change	—	—
Yeoh *et al.*[64]	44–50	Cervix	Decreased	Decreased	Decreased	Decreased
Iwamoto *et al.*[39]	8·5–9·5	Cervix	Increased	No change	—	Decreased
Kim *et al.*[65]	44–54	Cervix	No change	Decreased	—	Decreased
Yeoh *et al.*[66]	55–64	Prostate	Decreased	Decreased	Decreased	—
Yeoh *et al.*[38]	55–64	Prostate	No change	Decreased	No change	—

Reported studies are a mixture of retrospective and prospective investigations on different groups of patients undergoing different radiotherapeutic regimens. Varma *et al.* studied a group of ten patients with chronic radiation proctitis and symptoms of incontinence. This group had significantly lower resting anal canal pressures[18] and maximum tolerated rectal volumes[61] than asymptomatic matched controls. Studies of the acute[63] and chronic[62] effects of preoperative radiotherapy for rectal cancer showed no significant change in anal manometry at 4 weeks or at 14–42 (mean 35·5) months after treatment. Kim *et al.*[65] studied 24 patients with late radiation proctitis after treatment for carcinoma of the cervix, and found reduced squeeze pressures and rectal capacity but unchanged resting pressures in comparison to age-matched controls. A further study[39] performed during and 6 months after intracavitary radiotherapy for cervical cancer reported a significant reduction in maximum tolerated rectal volume and rectal compliance; the resting pressure increased.

Yeoh *et al.*[67] reported a reduction in anal resting and squeeze pressures, rectal compliance and maximum tolerated rectal volume in a randomly selected group of 15 women who had received pelvic radiotherapy 5–10 years previously. They then evaluated prospectively 34 patients having radiotherapy for prostatic carcinoma. At 6 weeks[66] and 1 year[38] after radiotherapy, nine patients (26 per cent) had faecal incontinence; faecal frequency and urgency were also significantly increased. Patients with urgency had lower threshold volumes to rectal distension. Reductions in resting and squeeze pressures at 6 weeks did not persist at 1 year.

It is perhaps of note that, although most studies report the total dose of radiation given, a large degree of variation exists in the way radiation is delivered, and consequently in the doses received by the anorectum. As there is no direct measurement of the dose received by the anorectum, the evidence is somewhat indirect and circumstantial.

Endoanal ultrasonography

Once again, the few studies reported represent a mixture of retrospective and prospective work on different groups of patients undergoing different radiotherapeutic regimens, and results have been inconclusive. A study of 35 patients treated for carcinoma of the prostate did not demonstrate any morphological changes in the internal anal sphincter (IAS) or external anal sphincter (EAS) at 4–6 weeks[66] or 1 year after treatment. A study including five patients, who had had radiotherapy to the rectum 3–6 months previously, demonstrated a significant increase in anal wall thickness (measured from the anal mucosa to the extreme portion of the EAS) compared with controls[68]. In Yeoh *et al.*'s retrospective study of patients who had been irradiated for cervical and endometrial carcinoma 5–10 years previously[67], four of 15 patients had reduced IAS thickness, although the EAS was unchanged.

Therapeutic options

Radiation-induced haemorrhagic proctitis

A number of chemopreventive agents have been investigated and treatment strategies include pharmacotherapy, hyperbaric oxygen, endoscopic techniques and surgery.

Chemoprevention

Eicosanoids and free radical release have been implicated in the pathogenesis of radiation damage. Mesalazine is a potent inhibitor of their synthesis in the mucosa and has therefore been tested as a chemopreventive agent. However, a multicentre double-blind placebo-controlled trial involving 153 patients failed to show any benefit over placebo in the prevention of acute radiation enteritis[69]. Another study suggests that compounds containing mesalazine may actually increase proctitis during radiation therapy[70].

Sucralfate, an aluminium hydroxide complex of sulphated sucrose, is believed to reduce microvascular injury and to promote angiogenesis through an action on mucosal basic fibroblast growth factor[71]. Oral sucralfate has been used prophylactically to reduce the incidence of proctitis, with mixed results in double-blind placebo-controlled trials[72–74]. A further double-blind controlled trial involving 86 patients using sucralfate enemas failed to show any significant benefit over placebo in the short term[75].

WR-2721 (amifostine) is an organic thyophosphate with radioprotective properties. Trials with both intravenous[76] and rectal[77] preparations have shown no benefit.

Misoprostol suppositories, used 1 h before each fraction of radiotherapy, were shown to be effective in reducing both acute and chronic proctitic symptoms in one prospective randomized study of 16 patients[78]. Larger studies are necessary before this strategy can be widely embraced.

Pharmacotherapy

Aminosalicylic acid derivatives, given orally or rectally, have not been shown to be of benefit in the treatment of radiation proctitis[79,80].

Steroids have been used to treat radiation proctitis both alone and in combination with other agents. Experiments in dogs investigating the value of oral prednisolone in treating the irradiated rectum showed it to be of no benefit[81]. Kochhar *et al.*[82] performed a small prospective randomized double-blind study comparing oral sulfasalazine and prednisolone enemas (15 patients) with oral placebo and sucralfate enemas (17 patients). Improvement was noted in both groups, but patients were significantly better by clinical criteria on the sucralfate regimen.

Topical sucralfate suspension has been reported by some authors[82–84] to be beneficial in acute and chronic proctitis. Of 26 patients treated with 20 ml 10 per cent sucralfate enema twice daily, 20 had a good response at 4 weeks and 24 at 16 weeks. At a mean of 45·5 months seven patients had further bleeding, again responding to further sucralfate therapy. Two patients required surgery to stop bleeding and ten had other complications, including rectal stricture (three), intestinal stricture (one), vaginal stenosis (one) and haematuria (six)[85].

Short-chain fatty acids are the main energy source for colonocytes and their utilization may be impaired in chronic radiation proctitis. It has been hypothesized that a plentiful supply of this substrate might prevent mucosal hypoplasia and progression to chronic inflammatory change. Pinto *et al.*[86] described their use in a double-blind randomized placebo-controlled trial in 19 patients. They were found to accelerate the healing process, with a significant early reduction in bleeding episodes and endoscopic scores. However, at 6 months no significant difference was demonstrable when compared with placebo. Another double-blind randomized placebo-controlled crossover study involving 15 patients performed by Talley *et al.*[24] found no benefit.

A 4 per cent formalin solution instilled into the rectum has been shown to be safe and effective in stopping bleeding in more than 75 per cent of cases, including those resistant to other therapies[20,87]. Saclarides *et al.*[87] reported a study of 16 patients with chronic haemorrhagic proctitis requiring transfusion and resistant to other treatments. Ten 50-ml aliquots of 4 per cent formalin were instilled into the rectum, aspirated, and the rectum was irrigated with saline between each aliquot. Bleeding stopped in all patients after one or more treatments. Two patients developed significant anal fissures and one also had significant tenesmus and reduced rectal capacity. Rectal instillation techniques have been carried out with and without anaesthesia. Formalin soaked on to gauze or a cotton-tipped applicator has been applied in the outpatient setting[88].

Hyperbaric oxygen

Hyperbaric oxygen therapy is thought to act by promoting neoangiogenesis and revascularization[89]. However, experience is limited as there are only a few centres with the facilities for this treatment. The largest study is by Warren *et al.*[90], who treated 14 patients in 100 per cent oxygen at two atmospheres. Symptoms resolved completely in eight patients, with significant improvement in a further one.

Endoscopic treatment

Endoscopic treatments appear to be most successful in controlling haemorrhage secondary to bleeding telangiectasia as opposed to diffuse haemorrhagic proctitis. Endoscopic bipolar electrocoagulation and heater probe treatment were effective (75 and 67 per cent respectively) in treating chronic bleeding from radiation telangiectasia in a randomized prospective study of 21 patients[91]. Response occurred within four treatment sessions and all patients reported improvement in quality of life.

Argon-beam coagulation has proved beneficial in three studies on seven[92], 28[93] and 14[23] patients with proctosigmoiditis resistant to medical therapy, although repeated treatments were often required. Neodymium yttrium–aluminium–garnet (NdYAG) laser treatment has also been shown to reduce bleeding in two studies of nine[94] and eight[95] patients. Again, multiple treatments were required, and in one study there were three complications of prolonged ileus. No other major complications were reported in the other endoscopic treatment studies described above.

Surgery

Surgery should be reserved for the minority of patients with intractable proctitis resistant to the above therapies[26,96]. Resection and coloanal pull-through may be possible[97–99] in patients who have retained good sphincter function. Allen-Mersh *et al.*[29] reported a successful result in eight of 11 patients using Park's technique. This involves resection of the diseased segment, stripping the rectal mucosa from the rectal remnant, and bringing healthy colon down through the 'rectal sleeve' to be anastomosed to the anal canal at the dentate line.

von Flue *et al.*[100] developed an ileocaecal reservoir to improve functional outcome. The ileocaecal segment was isolated on its lymphovascular pedicle, rotated counterclockwise and reanastomosed at the dentate line, thus providing a neorectal segment with intact intrinsic and extrinsic nerve and lymphovascular supply. Two patients were treated, with a good functional result; rectal capacity, compliance and anal manometry were similar to those in patients undergoing a low anterior resection for rectal cancer. A colostomy may be the preferred option where recurrent malignancy is expected[101], or in high-risk patients.

Radiation-induced rectal stricture

Endoscopic treatment

Although there have been isolated reports of endoscopic balloon dilatation and stenting for radiation-induced rectal stricture, no large series exists.

Surgery

As with other radiation-induced complications, restorative surgery should be considered only if the patient is otherwise healthy and cured of cancer, and if the operation can be performed safely with a satisfactory functional result. In suitable patients resection of the diseased segment with proximal defunctioning of the bowel is recommended[102], with a pull-through coloanal technique to avoid anastomosis to an ischaemic, irradiated rectum. Diversion alone should be performed in patients with suspected malignancy.

Radiation-induced rectovaginal fistula

Rectovaginal fistula is a distressing complication of pelvic radiotherapy, which can be emotionally and physically disabling[103]. The choice of treatment depends on the general state of the patient and the severity of symptoms. Most patients will need surgery and the choice is between a defunctioning stoma and local or resectional repair[104].

Conservative therapy

In a debilitated patient with minimal symptoms, aggressive treatment may be inappropriate. One report describes a conservative alternative to surgery using an occlusion device consisting of a nitinol wire frame with disc and anchoring portions and an intervening nylon patch[105]. This was only a pilot study and, although none of the seven patients included complained of faecal leakage, there have been no further reports of this technique.

Local repair of rectovaginal fistula

Fistula in the lowest third of the rectum is the most amenable to local repair, but this should be considered only in a healthy, compliant rectum. Progression of radiation damage, which may be subclinical at the time of operation, can result in late graft failure and/or fistula recurrence. A defunctioning stoma is usually employed, which may be raised months before the repair to allow the inflammatory process to resolve. The repair should be performed with healthy, non-irradiated tissues; conventional repair using local tissue should be avoided.

Interposition of a labial fat pad graft or Martius graft, although useful in the treatment of rectovaginal fistula in the non-irradiated setting[106], has had mixed reports when applied in an irradiated field[107,108]. Incorporation of well vascularized muscle, such as the gracilis, to separate the rectum and vagina was described in 1967 by Slot and Graham[109], but there are no recent reports of this technique for radiation-induced rectovaginal fistula.

An 'island flap' using a large pedicle flap of skin and adipose tissue supplied by the internal pudendal artery has been described by Kelemen and Lehoczky[110]. In a study of 30 patients with radiation-induced vesicovaginal and vesicovaginorectal fistula, only seven had vesicovaginorectal fistula, and in one of these the rectovesical component of the fistula persisted for 6 months after operation. No long-term results were reported.

Resectional procedures for rectovaginal fistula

In 1978 Parks *et al.*[111] described a 'sleeve anastomosis' for the treatment of rectovaginal fistula after irradiation. This initial study reported success in five patients. Nowacki[112] described a good functional outcome in 18 of 24 consecutive patients, with one postoperative death. A further large series adopting rectal resection and peranal sleeve anastomosis was reported by Cooke and de Moor[99]. Of the 37 consecutive patients with radiation damage to the rectum, 28 had rectovaginal fistula; technical success was achieved in 35, with no death. At 1 year, variable degrees of incontinence for liquid stool persisted in seven of nine patients with low rectovaginal fistula requiring a low anastomosis; those with a higher anastomosis were described as fully continent at 1 year. The functional success of the colonic J pouch following restorative proctectomy may also prove to be of benefit in patients with radiation injury, although the number of cases reported is small[26,113].

Soave's procedure, popularized for the treatment of Hirschprung's disease, was employed by Faucheron as an alternative method of restoring coloanal continuity after radiation complications in 15 patients and after surgical resection in a further 15. This operation avoids the need for pelvirectal dissection, as the mobilized left colon is brought down through the *in situ* rectum following a combined transabdominal and perineal rectal mucosectomy. Eighteen patients had a rectovaginal fistula at the time of surgery and three of these recurred after operation. One healed with conservative management, one healed after a defunctioning colostomy and one required a reanastomosis.

Other techniques include resection of the diseased segment and repair using a graft of sigmoid colon swung on its vascular pedicle[104] or a seromuscular intestinal graft used as a rectal patch[114]. The rectal patch has the advantage of avoiding an extensive pelvic dissection; the major disadvantage is that the diseased rectum is left in place. When advanced or recurrent malignancy is present, formation of a colostomy may be the most appropriate management[96].

Radiation-induced faecal incontinence

Many of the therapeutic options for faecal incontinence are contraindicated in patients with radiation damage to the rectum or anal canal. Conservative therapies include the use antidiarrhoeal agents such as loperamide[115] or codeine, but long-term medication may be an unsatisfactory solution for some patients. The use of pads may lead to further excoriation to radiation-damaged perineal skin and many patients find anal plugs uncomfortable[116]. Topical agents, such as phenylephrine cream which enhances normal IAS muscle function[117], have yet to be tested for radiation-induced incontinence.

Injectable bulking agents, such as cross-linked collagen, have had limited success when placed around a weakened IAS muscle[118] but this procedure may result in tissue breakdown in an irradiated area. Sacral nerve stimulation has not been tried in radiation-induced incontinence. It is believed to work, at least in part, through an alteration of local reflexes affecting rectal capacity and compliance[119,120]. This effect may be compromised in patients with chronic proctitis.

Surgical options for faecal incontinence due to a weakened IAS muscle have limited success rates. The long-term results of postanal repair are poor, with full continence rates as low as 21 per cent in some reported series[121] without the additional hazard of irradiated surgical tissue. An artificial anal sphincter has been implanted in one patient with radiation injury; this resulted in intense perineal pain which required removal of the device[122]. Radiation damage is now regarded as a contraindication to the use of this device; dynamic graciloplasty[123] is probably equally hazardous. The simplest surgical option for intractable faecal incontinence secondary to radiation injury is a colostomy.

Conclusion

Conservative treatment options after anorectal radiation injury are of limited value. Chemoprevention has been largely unsuccessful, although misoprostol deserves further investigation. Surgery should be a last resort and considered only when sphincter function is adequate, recurrent disease is excluded, and co-morbidity is not too great. Current knowledge of the effects of radiation therapy on the anorectum is based on a limited number of scientific studies, often involving small numbers of patients with variable periods of follow-up, and using delivery techniques that are now considered outdated. No accurate information on the dosage received by surrounding tissues is available. Prospective studies on large groups of patients with accurate dosimetric data and long-term follow-up are needed to provide comparable results. These may permit further modifications to delivery techniques and a subsequent reduction in the number of clinical complications.

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Randomized clinical trial of stapled *versus* Milligan–Morgan haemorrhoidectomy

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Background: The introduction of a stapling technique for the treatment of haemorrhoids has the potential for less postoperative pain, a short operating time and an early return to full activity. The outcome of stapled haemorrhoidectomy was compared with that of current standard surgery in a randomized controlled study.

Methods: Two hundred patients were randomized to either stapled haemorrhoidectomy ($n = 100$) or Milligan–Morgan haemorrhoidectomy ($n = 100$) between March 1997 and December 1998. Each patient received standardized postoperative analgesic and laxative regimens, and completed a linear analogue pain score every 6 h during the first day after operation, after the first motion and daily until the end of the first week. Operating time, frequency of postoperative analgesic intake, hospital stay, time to return to normal activity and postoperative complications were also recorded.

Results: The mean(s.d.) age of patients in the stapled and surgical groups was 44·1(3·2) and 49·1(12·2) years respectively. The stapled group had a shorter operating time, less frequent postoperative analgesia intake, shorter hospital stay and earlier return to normal activity. Early and late complications, and functional outcome were better in the stapled group.

Conclusion: Use of a circular stapler in the treatment of haemorrhoidal disease was safe, and was associated with fewer complications than conventional haemorrhoidectomy.

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Introduction

The treatment of third- and fourth-degree haemorrhoids is surgical. Many techniques have been proposed. Milligan–Morgan haemorrhoidectomy, as described in 1937, has remained the most popular[1,2]. Surgical haemorrhoidectomy has a reputation for being a painful procedure for a fairly benign disease[3]. It causes postoperative pain because of wide external wounds in the innervated perianal skin. Most patients need a 2–3-day postoperative hospital stay, with a convalescence of at least 1 month[1,3]. In late 1980s, several authors proposed haemorrhoidectomy with the use of mechanical suturing devices[4]. Rubber-band ligation, injection sclerotherapy, infrared photocoagulation and cryotherapy have been used with some success, but all have been shown to be inferior to surgery in the management of third- and fourth-degree haemorrhoids[2,5,6]. A few surgeons have used a circular stapler to excise redundant rectal mucosa in partial rectal prolapse[7–9]. More recently, Longo has advocated its use in the treatment of prolapsing haemorrhoids[10].

The introduction of stapled haemorrhoidectomy for the treatment of haemorrhoids has been met with a mixture of scepticism and interest[11]. The present study was designed to compare stapled haemorrhoidectomy with Milligan–Morgan haemorrhoidectomy with regard to operating time, postoperative pain, hospital stay, time to return to normal activity and postoperative complications.

Patients and methods

The study was conducted in Al-Mishary Hospital, Riyadh, Saudi Arabia from March 1997 to December 1998. Two hundred patients with different degrees of symptomatic prolapsing haemorrhoids underwent haemorrhoidectomy by either stapled or standard Milligan–Morgan haemorrhoidectomy. With the approval of the local ethics committee, patients were randomized into two equal groups of 100, based on a randomization list using a table of random numbers. Patients with prolapsed thrombosed piles, prolapse of one haemorrhoidal cushion, associated anal fistulas and anal fissures were excluded from this study.

Detailed written informed consent was obtained from all patients.

Patients were subjected to clinical examination, routine laboratory investigations and rectoanal manometry, using standard manometric equipment and techniques[12]. All patients received a phosphate enema and one dose of ceftriaxone in the morning of the day of surgery. Lactulose 20 ml was given twice daily for 10 days and metronidazole 400 mg three times daily for 7 days. All operations were performed in the lithotomy position under general endotracheal tube anaesthesia by the first author. The stapled procedure was performed according to the technique described by Longo[10]. A purse-string suture of 2/0 polypropylene was inserted at least 4 cm above the dentate line, catching only the mucosa and submucosa. A 33-mm circular stapling device (Proximate®; Ethicon Endo-surgery, Cincinnati, Ohio, USA) was opened to its maximum position and introduced through the anus. The purse-string suture was tied on the stapler shaft, and the head of the instrument was closed on the anvil incorporating the mucosal tissue in the purse string within the head of the gun. In women, the posterior vaginal wall was checked before firing the stapler to prevent entrapment. The stapler was then fired and gently withdrawn. The staple line was inspected for bleeding points. Haemostatic sutures were inserted before inserting a Spongostan® dressing (Ferrosan, Soeborg, Denmark). The excised tissue was sent for histopathological analysis. Patients randomized to Milligan–Morgan haemorrhoidectomy had preoperative infiltration with 20 ml 0·25 per cent bupivacaine hydrochloride and adrenaline 1 : 200 000. The conventional operative technique consisted of anal dilatation followed by retraction of the pile mass with an artery forceps, dissection, transfixion and division of the vascular pedicle. Good haemostasis was achieved, followed by insertion of anal Spongostan® dressing.

Postoperative analgesia consisted of pethidine hydrochloride 1·5 mg per kg body-weight intravenously for the first 24 h. Diclofenac, 50 mg orally and local lignocaine hydrochloride gel were given as required for 1 week. A visual analogue pain score was used, where 0 represented no pain and 10 represented the worst pain ever experienced. The pain score was recorded every 6 h during the first postoperative day, at the time of the first motion and daily until the end of the first week. The frequency and total doses of analgesic used during the first week after operation were recorded. Patients were discharged home once they required no further intravenous analgesia. They were reassessed at 7 days, 6 weeks, 6 months and at 1 year for effectiveness of symptom control and patient satisfaction. Rectoanal manometry was repeated for all patients after 6 months. The outcome measures were postoperative pain, operative time, frequency of analgesia intake, hospital stay, time to return to normal activity and wound healing, patient satisfaction and complications.

Table 1 Baseline patient characteristics

	Stapled	Surgical
Mean(s.d.) age (years)	44·1(3·2)	49·1(12·2)*
Sex ratio (M : F)	60 : 40	64 : 36
Clinical presentation		
Constipation	60	64
Bleeding	69	62
Discharge	39	30
Itching	34	30
Second-degree haemorrhoids	13	10
Third-degree haemorrhoids	32	30
Fourth-degree haemorrhoids	37	40
Prolapse	17	20

*P = 0·008 *versus* stapled (Student's t test for independent groups)

Statistical analysis

The data were analysed using BMDP Version PC90[13] (SPSS, Chicago, Illinois, USA). A comparison of baseline patient characteristics was carried out. Proportions and percentages were used to summarize categorical variables, while descriptive statistics such as mean(s.d.) were used for numerical variables. The χ^2 test was used to investigate the statistical significance of any categorical variables. Student's t test was used to compare the mean values of quantitative outcome measures between the two groups[14].

Results

Two hundred patients underwent haemorrhoidectomy during the study period. The mean(s.d.) age was 46·6(13·1) years, and 62 per cent were men. *Table 1* summarizes the patients' baseline demographic and clinical data. There was a significant difference in the mean age of patients between groups (P < 0·05), but no significant difference in the clinical presentation and gender. Outcome measurements for both techniques are presented in *Table 2*. The mean operating time was less for stapled than for conventional surgical haemorrhoidectomy (P < 0·001). The mean pain scores were significantly lower in the stapled group during the first 24 h, at the time of the first motion and at 1 week after operation. The mean frequency (number of doses) of analgesic intake per day was significantly less in the stapled group. In the stapled group, 51 per cent of patients did not require any analgesia, 33 per cent required only one injection, 6 per cent required two injections and 10 per cent required three injections of

Table 2 Postoperative outcome

	Stapled	Surgical	P*
Operating time (min)	9·0(2·7)	19·7(4·7)	< 0·001
Visual pain score			
First 24 h	2·5(1·3)	7·6(0·7)	< 0·001
First motion	1·1(0·3)	6·6(1·2)	< 0·001
1 week after operation	0·4(0·7)	2·6(0·6)	< 0·001
Postoperative analgesia (per day)	0·8(0·1)	3·7(0·8)	< 0·001
Hospital stay (days)	1·1(0·2)	2·2(0·5)	< 0·001
Time to wound healing (days)	7·0(1·2)	30·5(5·8)	< 0·001
Return to full activity (days)	8·2(1·9)	53·9(5·8)	< 0·001
Patient satisfaction (%)	92	80	

Values are mean(s.d.). *Mann–Whitney *U* test

Table 3 Manometric results before and after operation

	Preoperative	Postoperative	P*
Stapled			
Mean resting pressure	61·9(7·1)	60·3(6·3)	n.s.
Mean squeeze pressure	145·4(24·1)	142·8(22·2)	n.s.
Surgical			
Mean resting pressure	60·1(6·1)	42·7(4·6)	< 0·05
Mean squeeze pressure	147·2(20·7)	116·4(14·3)	< 0·05

Values are mean(s.d.). Postoperative pressure was decreased in the surgical group because of anal dilatation. n.s., Not significant. *Student's *t* test for paired samples

Table 4 Postoperative complications

	Stapled	Surgical
Bleeding	1	2
Retention of urine	7	14
Thrombosis (perianal)	3	3
Prolapse	1	2
Anal discharge	2	14*
Anal stenosis	2	5
Anal fissure	1	3
Skin tags	4	1

*$P = 0{\cdot}002$ *versus* stapled (Fisher's exact test)

analgesic. In the surgical group, all patients required analgesia to variable degrees. Histological examination of the specimens showed the presence of mucosa, submucosa and muscularis mucosa in 70 per cent of cases.

The rectoanal inhibitory reflex was present in all patients examined, both before and after operation. *Table 3* shows the resting and squeeze pressures of both groups before and 6 months after operation. In the stapled group the difference was not statistically significant, while in the surgical group both pressures were significantly reduced.

Early postoperative complications in the stapled group included acute urinary retention (seven patients), bleeding requiring suture ligation under general anaesthesia (one), external haemorrhoidal thrombosis (three) and posterior anal fissure (one). In the surgical group, postoperative complications included postoperative urinary retention (14), bleeding needing haemostasis under general anaesthesia (two) and external haemorrhoidal thrombosis (three) (*Table 4*).

Follow-up

At 6-month follow-up, all patients were available for assessment. Ninety-two per cent of patients in the stapled group were satisfied with their haemorrhoidal symptom control; two patients rated their symptom control as unsatisfactory owing to persistence of discharge and four patients complained of persistent skin tags. In the surgical group, 80 per cent of patients were satisfied with their haemorrhoidal symptom control. Fourteen patients rated their symptom control as unsatisfactory owing to persistence of discharge, one patient complained of persistent skin tags and anal fissure was reported in three patients. This responded well to conservative treatment.

At 1-year follow-up, 95 per cent of patients in the stapled group and 80 per cent in the surgical group were available for assessment. In the stapled group, a prolapse of one haemorrhoidal cushion had occurred in one patient and stenosis in two patients. These responded well to restapling in one case and outpatient proctoscopic anal dilatation in the other. In the surgical group, complications were prolapse of haemorrhoidal cushions in two patients and stenosis in five patients. Two cases of anal stenosis responded well to surgery while three improved after anal dilatation. No faecal incontinence was reported in either group.

Discussion

External and internal haemorrhoidal cushions are normal anatomical structures present from early embryonic life, which play an important role in accomplishing anal continence[15]. The cause of haemorrhoids is still debated. One theory is that mucosal prolapse of the anal canal results in elongation and kinking of the upper and middle haemorrhoidal vessels[3,15]. The surgical treatment of haemorrhoids by use of a circular stapler is an original technique introduced by Antonio Longo in 1993[10].

The stapled haemorrhoidectomy technique results in reduction of the mucosal prolapse, thereby restoring the normal anatomical relationship between the anal mucosa and the haemorrhoidal mass within the anal sphincter. This and interruption of the superior haemorrhoidal artery are suggested as the mechanisms by which stapling treats the haemorrhoids. It does not excise the haemorrhoids, but rather excises a circumferential column of mucosa and submucosa 2–3 cm above the dentate line, and then staples the defect. This enables the haemorrhoidal cushions to perform their physiological function to optimize continence[6,8,10,16].

There are relatively few reports that compare stapled haemorrhoidectomy with surgical haemorrhoidectomy; published data suggest that use of the stapler is less time consuming and is associated with less postoperative pain[17–19]. In the present study 200 patients were randomized to stapled or Milligan–Morgan haemorrhoidectomy and the results suggest that stapled haemorrhoidectomy is an effective treatment for symptomatic haemorrhoids with significant advantages. The mean operating time, postoperative linear analogue pain score and frequency of analgesic intake were significantly less than those in the surgical group. These results are comparable with previous data[3,7,8]. The reported healing time for open haemorrhoidectomy varies from 5 to 7 weeks[20]. In the present study, the mean time to healing of the anal wound in the stapled group was less than that in the surgical group. Healing of the anal wound was assessed in both groups by proctoscopic examination during follow-up.

Surgical haemorrhoidectomy reduces both continence to saline infusion and anal canal pressures[21–23]. In this study, there was a significant difference between the preoperative and postoperative anorectal pressure in the surgical group, but not in the stapled group. This may be due to anal dilatation during the surgical procedure. All patients in the stapled group have had effective symptom control with respect to prolapse, bleeding and discharge.

Molloy and Kingsmore[24] reported severe retroperitoneal sepsis after stapled haemorrhoidectomy and suggested routine antibiotic prophylaxis with this procedure. In this study, no patient developed sepsis. Prophylactic antibiotic in the form of ceftriaxone was given to all patients. Use of a transanal stapler during low colorectal anastomosis and sigmoidectomy is known to result in disordered continence as a result of internal sphincter injury[25,26]. This has raised some concerns regarding its use for treating haemorrhoids. Although damage to the internal anal sphincter has been reported with conventional haemorrhoidectomy, stapled haemorrhoidectomy did not cause any injury to the internal anal sphincter[8,10,27]. However, Cheetham *et al.*[28] reported that 31 per cent of patients developed pain and faecal urgency, which persisted for up to 15 months after stapled haemorrhoidectomy. They stated that the cause of this phenomenon is unclear, although incorporation of muscle in the doughnut may have a role. Alternatively it may result from placing the purse-string suture too close to the dentate line with accidental stapling of the sensitive anoderm and muscle impingement. This is difficult to understand as other authors have not found persistent pain after stapled haemorrhoidectomy[29,30]. In the present study, there was no persistent pain or faecal urgency in either group, as careful application of the stapler at least 2 cm above the dentate line was strictly adhered to in all cases.

Histological examination of the excised tissues confirmed the presence of mucosa, submucosa and muscularis mucosa in 70 per cent of cases and smooth muscle fibers, less than 1 mm in thickness, in 30 per cent. This muscle layer may belong to the muscular layer of the rectal wall rather than to the internal anal sphincter.

Long-term symptom control and functional outcome after surgical haemorrhoidectomy varies[31–33]. Recurrent haemorrhoidal symptoms are not uncommon. Thirty-three per cent of patients have recurrent bleeding[34]. The series of Milligan–Morgan haemorrhoidectomies reported by Bennett *et al.*[35] showed minor continence defects in 26 per cent of patients at 4-year follow-up. In the present study 1-year follow-up showed prolapse of a haemorrhiodal cushion in one patient and stenosis in two patients in the stapled group. Although the rate of anal stenosis in both groups was relatively high, it was similar to that reported previously[8,36–38]. Beattie *et al.*[8] stated that staple-line stenosis can occur if an inadequate width of mucosa is resected. In the event of staple-line stenosis treatment is by simple proctoscopic dilatation conducted in an outpatient setting[8].

In conclusion, use of a circular stapler in the treatment of haemorrhoids is safe, effective, causes minimal pain and is associated with fewer complications than conventional haemorrhoidectomy. It may replace traditional surgery for the treatment of haemorrhoids, but long-term follow-up is needed to determine whether these initial results are durable.

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Randomized clinical trial

Effect of *Helicobacter pylori* eradication on the ulcer recurrence rate after simple closure of perforated duodenal ulcer: retrospective and prospective randomized controlled studies

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Background: The possible advantage of eradication of *Helicobacter pylori* in patients with perforated duodenal ulcer is unknown. This study was planned to assess the prevalence of *H. pylori* after simple closure of a perforated duodenal ulcer and to study the effect of *H. pylori* eradication on ulcer persistence and recurrence.

Methods: Some 202 patients were followed prospectively for 2 years after simple closure of a perforated duodenal ulcer (prospective group). A second group of 60 patients was reviewed 5 years or more after perforation closure (retrospective group). The prevalence of *H. pylori* in patients with perforated duodenal ulcer was compared with that in controls. Patients in the prospective group were randomized to receive either ranitidine alone or quadruple therapy (ranitidine, colloidal bismuth subcitrate, metronidazole and tetracycline) after operation. The incidence of *H. pylori* infection after the two treatments and the association with residual or recurrent ulcer were studied. In the retrospective group long-term ulcer recurrence was correlated with *H. pylori* status.

Results: The prevalence of *H. pylori* in patients with perforated duodenal ulcer was not significantly different from that in controls. At every interval of follow-up in the prospective group and in the retrospective group the *H. pylori* infection rate was significantly higher in patients who had recurrent or residual ulcers.

Conclusion: Eradication of *H. pylori* after simple closure of a perforated duodenal ulcer should reduce the incidence of residual and recurrent ulcers.

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Introduction

Primary treatment of a perforated duodenal ulcer involves either patch closure or definitive surgery for the ulcer. Simple closure is associated with an unacceptably high recurrence rate of duodenal ulcer, as high as 42–50 per cent in some series[1]. Alternatively, definitive surgery may have long-term side-effects in patients who might otherwise have been cured by simple closure alone[2].

Use of H_2 blocking drugs and proton pump inhibitors to reduce ulcer recurrence after simple patch closure has produced conflicting results[2–4]. Attention has recently focused on the role of *Helicobacter pylori* in perforated duodenal ulcer. At present there are only few reports on the significance of *H. pylori* infection in perforated duodenal ulcer[5–8], only one of which has addressed the effect of eradication of *H. pylori* on the natural history of perforated duodenal ulcer[8]. If *H. pylori* infection was proved to cause ulcer recurrence, eradication of this organism would become imperative after patch closure. The aim of this study was to determine the prevalence of *H. pylori* in patients with a perforated duodenal ulcer and to correlate *H. pylori* status with the short-, medium- and long-term ulcer recurrence rates following simple closure.

Patients and methods

Informed consent was obtained from all patients for inclusion in the study. The Institute Ethics Committee approved the study. The study population consisted of two groups: a prospective group of 202 patients with perforated duodenal ulcer followed for 2 years after patch closure and a retrospective group of 60 patients who had patch closure 5 years or more earlier and who were recalled to establish healing and recurrence of ulcer with respect to *H. pylori* status. Patients who underwent immediate definitive surgery were excluded from the study. In all patients the perforation was closed with o/o polyglactin (Vicryl; Ethicon, Somerville, New Jersey, USA) over an omental patch. The prospective group of patients was randomized into two groups using a random number table and sealed envelope technique. The first group received ranitidine alone and the second received quadruple therapy.

Patients in group 1 received oral ranitidine 150 mg twice daily as soon as they were able to take oral fluids and continued for 4 weeks. Patients in group 2 were administered quadruple therapy consisting of ranitidine 150 mg twice daily, colloidal bismuth subcitrate 120 mg four times daily, metronidazole 400 mg three times daily and tetracycline 500 mg four times daily. All patients were called for personal interview and detailed follow-up evaluation including endoscopy every 6 months for 2 years. At each endoscopy, mucosal ulceration of 5 mm or more in the duodenum was considered as persistent or recurrent ulceration[9]. Ulcer healing was defined as either complete re-epithelialization of the duodenal mucosa or the presence of a scar[10]. At each follow-up visit a urease test was performed, and endoscopic mucosal biopsies from the pyloric antrum and the gastric body were examined histologically to determine *H. pylori* status. Two biopsies from each site were taken for each test. Gastric biopsies were necessary to assess *H. pylori* status following treatment owing to the possibility of proximal migration of the organism[11]. Patients who had undergone patch closure of a perforated duodenal ulcer 5 years or more before the study constituted the retrospective group. The patients all underwent endoscopy.

In both the prospective and retrospective groups of patients the prevalence of *H. pylori* was correlated with sex, size of the perforation, smoking and alcohol intake. The prevalence of *H. pylori* in both groups was related to ulcer recurrence.

One hundred volunteers admitted for non-gastrointestinal disorders were included in the study as hospital-based controls. They had given consent to participate in a separate study to assess the prevalence of *H. pylori* in individuals without gastrointestinal disorders. Gastrointestinal disorders were ruled out by clinical examination and endoscopy. The controls were of similar age and sex to the patients with perforation, although strict matching was not possible. Logistic regression analysis was carried out to adjust for age and sex.

Helicobacter pylori infection

H. pylori status was determined by measurement of serum levels of anti-*H. pylori* immunoglobulin (Ig) G using enzyme-linked immunosorbent assay (ELISA), at presentation with a perforated ulcer and at 8 weeks after perforation closure in the prospective group. The possibility that acute perforated duodenal ulceration could be associated with an early phase of *H. pylori* infection before IgG seroconversion necessitated repeat serology at 8 weeks[7]. Serology was carried out with a validated second-generation Microwell ELISA using purified solid-phase antigens (UBI Magiwell™; United Biotech, Mountain View, California, USA). Endoscopy, urease test and histology were not done at the time of perforation closure. During follow-up visits histological examination was carried out with the Giemsa stain and a urease test was performed using a urease solution prepared and standardized in this institution[12]. Eradication was defined as a negative urease test and negative histology for *H. pylori*. In the retrospective group of patients with perforated duodenal ulcer and in control subjects the prevalence of *H. pylori* infection was established by urease test, histology and serology. A positive result for any two of the three tests was taken to indicate *H. pylori* infection[13].

Statistical analysis

Data were analysed using Epi Info™ Software (Version 6.04, Centres for Disease Control and Prevention, Atlanta, Georgia, USA)[14]. Logistic regression analysis was done using SPSS for Windows (Version 6.0) (SPSS, Chicago, Illinois, USA). χ^2 test and Fisher's exact test (when the individual value in any cell was less than five) were used to correlate the prevalence of *H. pylori* in perforated duodenal ulcer with variables such as size, smoking and alcohol use. These tests were also used for comparison of the effect of ranitidine and quadruple therapy on eradication of *H. pylori* and for correlation of eradication with ulcer recurrence. When a significant difference was noted, logistic regression analysis was done to adjust for age and sex. For all tests, a calculated alpha value of less than 5 per cent was considered significant.

Results

The control group consisted of 82 men and 18 women of mean(s.e.m.) age 41·1(1·5) (range 18–75) years. Sixty-nine (69 per cent) of these subjects were positive for *H. pylori* compared with 148 (73 per cent) of 202 patients in the prospective group with perforated duodenal ulcer (P = 0·52). In the retrospective group, 32 (53 per cent) of the 60 patients had *H. pylori* infection (P = 0·07 *versus* controls). Overall, there were only seven women in a total of 202 patients with perforated duodenal ulcer in the prospective group and three of 60 in the retrospective group, consistent with the sex difference in ulcer disease in this part of the country. The prevalence of *H. pylori* infection was 73 per cent in men *versus* 71 per cent (five of seven) in women in the prospective group ($P = 0.6$) and 56 per cent *versus* zero in the retrospective group ($P = 0{\cdot}19$). Size of perforation, smoking, alcohol use and intake of non-steroidal anti-inflammatory drugs (NSAIDs) did not affect *H. pylori* status (*Table 1*).

Eradication rate in randomized study

A comparison between the eradication rates achieved with ranitidine or quadruple therapy at different follow-up intervals is shown in *Table 2*. Only the patients with *H. pylori* infection at presentation were included in this analysis. At each follow-up interval the eradication rate was higher with quadruple therapy than with ranitidine alone. In the quadruple therapy group the eradication rate dropped from 80 per cent at 8 weeks to 33 per cent at 2 years, whereas in the ranitidine group it fell from 57 to 29 per cent at corresponding intervals. However, the difference between ranitidine and quadruple therapy reached statistical significance only at 8 weeks ($P = 0{\cdot}01$).

Helicobacter pylori infection and ulcer recurrence

Table 3 shows a correlation between the *H. pylori* infection rate and the presence of recurrent or residual ulcer at various intervals after perforation closure. The *H. pylori* infection rate was significantly higher in patients with recurrent or residual ulcer for up to 18 months. The infection rate varied between 76 and 94 per cent in those with a persistent ulcer, and between 11 and 38 per cent in those who had no residual ulcer. At 2 years, although the *H. pylori* infection rate in patients with recurrent or residual ulcer was 86 per cent compared with 42 per cent in those with a healed ulcer this was not significant owing to the small number of patients. The difference between the two groups remained significant after adjustment for age and sex by logistic regression analysis.

During follow-up of patients with *H. pylori* infection the risk of having an ulcer ranged from 55 to 70 per cent at the different time intervals. In patients with no *H. pylori* infection, the risk of ulcer was low, between 4 and 28 per cent.

In the retrospective group, the rate of *H. pylori* infection was 90 per cent (26 of 29) in patients with a recurrent ulcer compared with 19 per cent (six of 31) in those with no ulcer ($P < 0{\cdot}0001$). When adjusted for age and sex, the higher prevalence in patients with recurrent ulcer was maintained. In patients with *H. pylori* infection the risk of an ulcer being present was 81 per cent (26 of 32) compared with 11 per cent (three of 28) in those without infection.

Table 1 Correlation of *Helicobacter pylori* status with variables associated with perforated duodenal ulcer

	No. with *H. pylori* infection	*P*
Prospective group (*n* = 202)		
Size of perforation (mm)		0·15
< 5	106 (70)	
6–10	30 (79)	
> 10	12 (92)	
Smoker		0·90
Yes	38 (72)	
No	110 (74)	
Alcoholic		0·35
Yes	35 (67)	
No	113 (75)	
Retrospective group (*n* = 60)		
Size of perforation (mm)		0·82
< 5	18 (50)	
6–10	10 (59)	
> 10	4 (57)	
Smoker		0·87
Yes	11 (52)	
No	21 (54)	
Alcoholic		0·77
Yes	9 (60)	
No	23 (51)	

Values in parentheses are percentages

Table 2 Comparison of *Helicobacter pylori* eradication rates between ranitidine and quadruple therapy in patients with perforated duodenal ulcer studied prospectively

Follow-up	*H. pylori* eradicated	*P*
8 weeks		
Ranitidine (*n* = 60)	34 (57)	0·01*
Quadruple (*n* = 64)	51 (80)	
6 months		
Ranitidine (*n* = 50)	25 (50)	0·29*
Quadruple (*n* = 53)	33 (62)	
12 months		
Ranitidine (*n* = 37)	15 (41)	0·41*
Quadruple (*n* = 40)	21 (52)	
18 months		
Ranitidine (*n* = 15)	3 (20)	0·25†
Quadruple (*n* = 19)	7 (37)	
24 months		
Ranitidine (*n* = 7)	2 (29)	0·66†
Quadruple (*n* = 6)	2 (33)	

Values in parentheses are percentages. Only patients with *H. pylori* infection at presentation were included. *χ^2 test; †Fisher's exact test

Table 3 Correlation of *Helicobacter pylori* infection status at follow-up with incidence of residual or recurrent duodenal ulcer

Follow-up	No. of patients	*H. pylori* infection	*P*
Prospective group			
8 weeks			
Ulcer present	40	32 (80)	< 0·0001*
No ulcer	122	14 (11)	
6 months			
Ulcer present	47	42 (89)	< 0·0001*
No ulcer	95	28 (29)	
12 months			
Ulcer present	33	31 (94)	< 0·0001†
No ulcer	67	24 (36)	
18 months			
Ulcer present	21	16 (76)	0·029*
No ulcer	21	8 (38)	
24 months			
Ulcer present	7	6 (86)	0·08†
No ulcer	12	5 (42)	
Retrospective group			
Ulcer present	29	26 (90)	< 0·0001*
No ulcer	31	6 (19)	

*χ^2 test; †Fisher's exact test

Discussion

A few published studies have suggested a significant relationship between perforated duodenal ulcer and *H. pylori* infection. Sebastian *et al.*[6] reported *H. pylori* in 24 of 29 patients with perforated peptic ulcer by the urea breath test done on the eighth day after operation. At 6 weeks' follow-up all patients with persistent duodenal ulcer were positive for *H. pylori* infection and they recommended eradication therapy for all patients with perforated peptic ulcer associated with this organism[6]. Ng *et al.*[15] noted that 70 per cent of patients with perforated duodenal or prepyloric ulcers were infected with *H. pylori*. This rate was not significantly different from the 55 per cent seen in the local population. However, when subclassified into NSAID users and non-users, 80 per cent of non-NSAID-related perforations were associated with *H. pylori* infection compared with only 23 per cent of those in NSAID users. The authors concluded that *H. pylori* played an important role in the pathogenesis of non-NSAID-related perforated duodenal ulcer[15].

Chu *et al.*[16] from Hong Kong found *H. pylori* in only 47 per cent of patients with past duodenal ulcer perforations. Even though fewer than half their patients were infected with *H. pylori*, it was considered an independent risk factor for recurrent ulceration. Another Japanese study reported a higher density of *H. pylori* in patients with perforated peptic ulcer than in others with bleeding and stenotic ulcers[17]. A recent report from Hong Kong randomized patients with perforated duodenal ulcers to receive either omeprazole alone or a quadruple anti-*H. pylori* therapy[8]. At 1-year follow-up ulcer relapse was 38 per cent in the omeprazole group compared with 5 per cent in the group receiving anti-*H. pylori* therapy.

Other reports document contradictory findings. Jensen *et al.*[5] reported an *H. pylori* prevalence rate of only 48 per cent in patients with acute perforated duodenal ulcer. Reinbach *et al.*[7] found no significant difference in *H. pylori* infection rate between patients with perforated duodenal ulcer and controls (47 *versus* 51 per cent). In another study from India, none of the patients with a duodenal ulcer perforation showed *H. pylori* infection[18]. Debongnie *et al.*[19] found that their prevalence of 56 per cent in patients with perforated gastroduodenal ulcers lay between that seen in healthy blood donors (36 per cent) and their patients with uncomplicated peptic ulcers (86 per cent). In most of the above mentioned studies, other than the paper by Ng *et al.*[8], the number of patients was limited and few addressed the question of eradication of *H. pylori*. In the present studies serology was used to determine *H. pylori* infection as it is least invasive, and accurate except in recently treated patients[7,20]. A second serological test at 8 weeks was necessary to identify patients who were in the early phase of seroconversion at the time of perforation. Another advantage of serology is that postoperative treatment with antibiotics for peritonitis in the postoperative phase would not affect the results because serum IgG levels take several months to decline or disappear.

As the maximum follow-up possible in the prospective group was only 2 years, a retrospective cohort was included to determine the association between a positive *H. pylori* status and ulcer recurrence in the long term.

Standard triple therapy was used in this study as it is considered a gold standard for *H. pylori* eradication in the absence of sensitivity reports[21]. Ranitidine was given to both groups as it was considered unethical to leave patients with a proven ulcer without antisecretory therapy. At every interval of follow-up eradication rates were higher after quadruple therapy than after ranitidine alone. However, beyond 8 weeks there was no significant difference in the eradication rate between the two regimens. The high eradication rate at 8 weeks following quadruple therapy probably results from suppression of the organism, allowing its recrudescence at subsequent follow-up. Antimicrobial resistance to metronidazole could also be one of the factors responsible for the low and decreasing eradication rates with longer follow-up. An Asian report has shown metronidazole resistance in 50 per cent of all strains of *H. pylori* in Singapore and Hong Kong, and in 80–90 per cent of all strains in India[21]. This high antimicrobial resistance to nitroimidazoles might be the cause of the difference in eradication rates in Asia compared with the West. Replacement of ranitidine with omeprazole did not affect the low eradication rate with metronidazole-containing regimens[22].

The *H. pylori* infection rate was significantly higher in the prospective group at all intervals of follow-up to 2 years in patients with recurrent or residual ulcer after closure of a duodenal ulcer compared with that in patients in whom the ulcer remained healed. In the retrospective group 90 per cent of patients with a recurrent ulcer had *H. pylori* infection compared with only 19 per cent in those with no ulcer. This suggests an association between *H. pylori* infection and recurrent duodenal ulcer disease in the short, intermediate and long term. It appeared that a negative *H. pylori* infection status was more useful in predicting a healed ulcer than a positive *H. pylori* status was in indicating the possibility of recurrent ulcer.

Recurrence or relapse of a duodenal ulcer following simple closure of perforated duodenal ulcer is significantly related to *H. pylori* infection. Eradication of *H. pylori* should therefore be recommended in all patients with a perforated duodenal ulcer and *H. pylori* infection.

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Randomized study comparing cardiac response in endovascular and open abdominal aortic aneurysm repair

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Background: The aim was to compare the cardiac response and the incidence of adverse cardiac events during and after endovascular (EVAR) and open (OR) repair of abdominal aortic aneurysms (AAAs).

Methods: Seventy-six patients with an AAA suitable for EVAR, and in a general condition allowing open surgery were randomized to EVAR (57 patients) or OR (19 patients). The analysis was on an intention-to-treat basis. Haemodynamic variables were assessed intraoperatively before, during and after aortic occlusion. During the procedure myocardial ischaemia was identified with use of electrocardiography (ECG) and transoesophageal echocardiography (TEE). After operation, cardiac complications were diagnosed by clinical observation, 12-lead ECG at 1 h, 1 day and 7 days, echocardiography at 1 month and measurement of cardiac enzymes.

Results: After aortic occlusion, a greater decrease in systemic vascular resistance compared with baseline was observed with OR than with EVAR (– 396 and – 70 dyne s/cm^5 respectively; $P = 0{\cdot}03$). The stroke work index, as a direct measure of myocardial performance, demonstrated a decrease during OR and an increase during EVAR during aortic occlusion (– 6·6 and + 1·7 g m/m^2 respectively; $P = 0{\cdot}03$) as well as after aortic occlusion (– 7·6 and + 3·4 g m/m^2 respectively; $P < 0{\cdot}01$), compared with baseline. The incidence of postoperative clinical cardiac complications was comparable in the two study groups; however, myocardial ischaemia, as observed by ECG and TEE, was observed more frequently in the OR group (ten of 19 *versus* 15 of 57 patients; $P = 0{\cdot}05$).

Conclusion: Haemodynamic changes were less severe and there was a lower incidence of myocardial ischaemia during EVAR than during OR. Studies are needed to demonstrate whether this may reduce the operative mortality rate.

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Introduction

Endovascular abdominal aortic aneurysm (AAA) repair (EVAR) has been developed as an alternative to open aneurysm repair (OR). This technique has become increasingly popular among physicians and patients, despite a paucity of scientific proof of a significant reduction in the main adverse outcome events. Before its widespread use can be recommended, it must be established whether endovascular repair is equivalent to or better than open surgery. The main primary outcome events that should be compared are perioperative mortality and morbidity rates. Of early complications, cardiac problems are among the most severe and frequent following conventional surgery. As many as 60 per cent of all perioperative deaths are from cardiac causes[1–3].

Accurate comparison of postoperative cardiac events requires a prospective randomized trial, involving a large number of patients. Results of such studies are not available at the present time. The purpose of this study was to compare the cardiac and haemodynamic response, and occurrence of myocardial ischaemia associated with EVAR and OR in an institutional randomized trial.

Patients and methods

The institutional review boards of the Catharina Hospital and St Joseph Hospital approved the protocol of the Eindhoven Stent Prosthesis for Aneurysm Study in September 1996. Between September 1996 and October 1999, all patients who required treatment for an AAA larger than 50 mm were considered for enrolment. Exclusion criteria were adverse aneurysm morphology for endografting, contrast allergy, medical conditions precluding open surgery and refusal of the patient to participate in the study.

Randomization of patients to treatment

After completion of the preoperative investigations informed consent for the study was obtained, and patients were randomized to one of the two treatment groups. Randomization was performed with a 3 : 1 ratio for EVAR and OR respectively. This scheme was used because randomization into equal groups would reduce the experience of the team involved with the endovascular technique and because it was expected that this randomization scheme would encourage patients to enrol as the chance of being allotted to endovascular treatment was higher.

Data in the literature indicate that about 45 per cent of aortic procedures are accompanied by signs of myocardial ischaemia (clinical, on electrocardiography (ECG) or on transoesophageal echocardiography (TEE))[4–7]. It was anticipated that stent-graft procedures would be comparable with peripheral vascular reconstructions with regard to their impact on haemodynamics and myocardial performance, and accompanied by signs of myocardial ischaemia in about 10 per cent[4–7]. At this assumed difference of 35 per cent, power calculations showed that group sizes of 57 and 19 for EVAR and OR respectively would enable the study to demonstrate differences (two-tailed, $\alpha = 0{\cdot}05$) in the incidence of myocardial ischaemia at slightly greater than 80 per cent.

During the 3 years of enrolment, 70 patients had EVAR. Thirteen of these were not randomized because of poor medical condition, refusal to participate in the study, or because of referral for EVAR from another region.

Preoperative cardiac assessment

All patients were seen before operation by one of two cardiologists, for a thorough medical history and clinical examination. The evaluation included standard 12-lead ECG and a dobutamine stress echocardiogram (DSE). For DSE analysis the wall motion score was calculated by the summation of the segmental wall motion scores of 13 left ventricular segments. Each segmental score was graded on a five-point scale, ranging from –1 for hyperkinesia, to 0 for normokinesia, 1 for hypokinesia, 2 for akinesia and 3 for dyskinesia[8].

Operative and postoperative management

All patients underwent standardized general anaesthesia with endotracheal intubation. For the induction, etomidate, pancuronium and fentanyl were used; anaesthesia was subsequently maintained by nitrous oxide and oxygen gas mixture, and fentanyl and pancuronium as needed. Continuous radial artery pressure was monitored. Electrocardiographic recording of the I–II–V5/6 leads for heart rate and ST-segment analysis was continued until discharge from the intensive care unit. A Swan–Ganz catheter was used to measure pulmonary wedge pressure, systemic vascular resistance (SVR), cardiac index and left ventricular stroke work index (SWI). All intraoperative measurements were performed at three time points: 10 min before (baseline), during and 5 min after aortic occlusion. The EVAR procedures were performed according to a technique described previously[9]. During EVAR, inflation of a latex balloon within the aorta (when Stentor (Mintec, La Ciotat, France), Vanguard (Boston Scientific, Natick, Massachusetts, USA) or Lifepath (Baxter, Irvine, California, USA) systems were used) or deployment of the aortic part of the device until the point at which the aorta was occluded (when an AneuRx (Medtronic, Santa Rosa, California, USA) device was used) determined the time of aortic occlusion. During the same three intervals, myocardial performance was assessed by TEE to record any signs of left ventricular wall motion abnormalities. TEE images were recorded on to video tape and reviewed off-line by a second cardiologist, who was blinded to the type of operation performed. Standard OR was performed via a transabdominal approach and aortic occlusion was determined by infrarenal clamping time.

To enable accurate recording of all cardiac events, patients were admitted to the intensive care unit, and cardiac monitoring was continued until at least 24 h after the operation. Twelve-lead ECG was perfomed at 1 h, 1 day and 1 week after operation. Blood samples for measurement of cardiac enzymes (creatinine kinase, creatinine kinase-MB, lactate dehydrogenase and aminotransferase) were obtained 24 h after operation. One month after the procedure a transthoracic echocardiogram was repeated and compared with the preoperative study.

Outcome events

The following endpoints were recorded and analysed: death from all causes, cardiac death, myocardial infarction and congestive heart failure; a composite outcome of all the cardiac events was also analysed. Endpoints obtained at cardiac assessment included: ST abnormality on ECG, wall motion abnormality on TEE and combined outcome of an abnormal ECG/TEE. The diagnosis of myocardial ischaemia was based on the detection of ST abnormalities on ECG and the observation of new wall motion abnormalities on TEE.

ST abnormality was defined as ST segment depression of 0·5 mm or more, or ST segment elevation of 2 mm or greater in the precordial leads and of 1 mm or more in all other leads compared with the baseline reading, and lasting for at least 1 min. Regional wall motion abnormalities, as identified at intraoperative TEE, were defined as a change of 2 or greater in wall motion score in one or more of the 13 segments of the left ventricle compared with a previous echocardiogram. The definition of myocardial infarction was based on the existence of at least one of the following criteria: an ST abnormality combined with an increase in cardiac enzymes to greater than twice the normal level or persisting ventricular wall motion abnormality at echocardiography 1 month after operation. Congestive heart failure was present if symptoms or signs of pulmonary oedema were observed; chest radiography showed vascular redistribution, interstitial and alveolar oedema; signs of new heart failure developed (cardiomegaly, S3 gallop, jugular venous distension, peripheral oedema); or there was a change in cardiac medication.

Statistical analysis

The different outcome events in the two study groups were compared according to the intention-to-treat principle. Data were expressed as mean(s.e.m.) unless stated otherwise. Categorical data were compared between groups by χ^2 analysis or Fisher's exact test; *t* tests were used for continuous variables with approximately normal distribution and the Mann–Whitney non-parametric test was used to compare other continuous variables. Wilcoxon's signed rank test was used for analysis of paired data. The limit of statistical significance was set at $P = 0·05$ (two sided). Data analysis was performed by use of the statistical software SPSS for Windows 7.0 (SPSS, Chicago, Illinois, USA).

Results

Preoperative, operative and postoperative course

Seventy-six patients were randomized to EVAR (57 patients) and OR (19 patients). Patient demographics and risk factors were similar in the two groups (*Table 1*). The results of preoperative DSE, in particular the wall motion scores before and after dobutamine-induced stress, were comparable between the study groups. An unfavourable myocardial contractility with a baseline wall motion score of 10 or more was observed in 13 patients (nine and four patients having EVAR and OR respectively). In 12 patients significant coronary disease was suspected by an increase in wall motion score of more than 2 (nine and three patients having EVAR and OR respectively) and with typical complaints during dobutamine stress (six patients, all having EVAR). These observations were equally distributed between the two study groups.

Table 1 Patient characteristics

	EVAR (*n* = 57)	OR (*n* = 19)
Age (years)*	69 (52–82)	68 (52–81)
Sex ratio (F : M)	3 : 54	3 : 16
Maximum AAA diameter (mm)*	56 (52–84)	52 (40–61)
ASA classification†		
II	34 (60)	15 (79)
III	23 (40)	4 (21)
History of myocardial infarction	18 (32)	7 (37)
Previous PTCA	7 (12)	2 (11)
Previous CABG	13 (23)	5 (26)
History of coronary artery disease	25 (44)	10 (53)
Hypertension‡	31 (54)	12 (63)
Smoking‡	26 (46)	5 (26)
Diabetes‡	8 (14)	4 (21)
COPD‡	17 (30)	4 (21)

*Values are mean (range); other values in parentheses are percentages. Three patients with an aneurysm between 40 and 50 mm were included; these aneurysms either caused distal embolization (one patient) or were associated with large (40 and 55 mm) common iliac aneurysms (two patients). †American Society of Anesthesiologists (ASA) classification[10]. ‡Society for Vascular Surgery and International Society for CardioVascular Surgery risk score >0[11]. EVAR, endovascular repair of abdominal aortic aneurysm (AAA); OR, open AAA repair; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease

Table 2 Procedural data in the two study groups

	EVAR (*n* = 57)	OR (*n* = 19)
Clamping time (min)	–	50 (33–80)
Duration of operation (min)	180 (65–320)	180 (120–270)
Packed cell transfusion (no.)	0 (0–8)	2 (0–5)
Duration of intubation (h)	7 (0–47)	10 (0–360)
Intensive care stay (h)	19 (8–90)	21 (16–360)
Return to normal feeding (days)	2 (1–11)*	5 (3–7)
Hospital stay (days)	5 (2–21)*	11 (8–50)

Values are median (range). EVAR, endovascular repair of abdominal aortic aneurysm (AAA); OR, open AAA repair. $^*P < 0·01$ *versus* OR (Mann–Whitney *U* test)

Observations from preoperative tests led to therapeutic measures in several patients. A change of preoperative medication was made in 11 patients and supplementary intraoperative medication was given to 16. In case glyceryl trinitrate was used for afterload reduction during aortic occlusion, administration was discontinued well before clamp release. Before aneurysm repair coronary angioplasty was performed in one patient and a coronary bypass in two

Table 3 Haemodynamic variables relative to aortic occlusion during endovascular and open aneurysm repair

	EVAR ($n = 57$)			OR ($n = 19$)		
	Before	During	After	Before	During	After
Heart rate (per min)	63(2)	65(2)	63(2)	65(3)	60(4)	65(3)
Mean blood pressure (mmHg)	76(2)*	79(2)	79(2)	90(5)	80(4)	74(3)
Systemic vascular resistance (dyne s/cm^5)	1171(64)	1099(53)	1103(55)†	1304(131)	1247(117)	907(80)‡
Pulmonary wedge pressure (mmHg)	13(1)	15(1)	15(1)	14(2)	12(1)	16(1)
Cardiac index (l per min per m^2)	2·6(0·1)	2·8(0·1)	2·9(0·1)‡	2·7(0·2)	2·6(0·2)	3·2(0·2)‡
SWI (g m/m^2)	36(2)*	37(2)	39(2)‡	46(4)	39(3)	38(4)‡

Values are expressed as mean(s.e.m.). Measurements were made before, during and after aortic occlusion. EVAR, endovascular repair of abdominal aortic aneurysm (AAA); OR, open AAA repair; SWI, left ventricular stroke work index. $^{*}P = 0{\cdot}02$, $^{\dagger}P = 0{\cdot}05$ *versus* OR (*t* test); ‡significant intragroup difference *versus* baseline (Wilcoxon's signed rank test)

Table 4 Changes from baseline in haemodynamic variables during and after aortic occlusion within the two study groups

	Changes during aortic occlusion		Changes after aortic occlusion	
	EVAR	OR	EVAR	OR
Systemic vascular resistance (dyne s/cm^5)	− 60(56)	− 24(134)	− 70(58)*	− 396(130)
Cardiac index (l per min per m^2)	0·2(0·1)	− 0·1(0·1)	0·3(0·1)	0·4(0·2)
SWI (g m/m^2)	1·7(1·5)*	− 6·6(3·1)	3·4(1·6)†	− 7·6(3·0)

Values are mean(s.e.m.) changes occurring during aortic occlusion (value during occlusion − preocclusion value) and after aortic occlusion (value after occlusion − preocclusion value). EVAR, endovascular repair of abdominal aortic aneurysm (AAA); OR, open AAA repair; SWI, left ventricular stroke work index. $^{*}P = 0{\cdot}03$, $^{\dagger}P < 0{\cdot}01$ *versus* OR (*t* test)

patients (one having EVAR and two OR). One of these patients, while recovering from the coronary bypass operation, had to undergo urgent open AAA repair because of aneurysm rupture. This patient had been randomized to EVAR and was therefore analysed as belonging to this treatment group.

Open surgery consisted of aneurysm replacement by a tube prosthesis in 16 patients and a bifurcated prosthesis in three. EVAR was done using a bifurcated prosthesis in all cases. A Stentor device was used in three patients, a Vanguard device in 22, an AneuRx in 30 and a Lifepath prosthesis in one patient. Excluding the patient with a rupture there were no other conversions to open surgery in patients randomized to EVAR.

Operating times and duration of stay in intensive care were comparable between the two groups (*Table 2*). Patients in the EVAR group had a faster return to normal feeding and a shorter hospital stay than those who had OR.

Haemodynamic changes

Baseline values of blood pressure and SWI were significantly lower in patients who had EVAR (*Table 3*). The postocclusion SVR was lower in patients who had OR than in those who underwent EVAR. The intraoperative changes in baseline variables are indicated in *Table 4*. SVR decreased significantly after aortic occlusion during OR, while it was fairly stable in patients who had EVAR ($P = 0{\cdot}03$, group difference in change). The cardiac index increased significantly after aortic occlusion in both study groups. There was a significant increase in SWI after aortic occlusion in the EVAR group, but a significant fall in the OR group.

Clinical cardiac complications

Two patients (2 per cent) died within 30 days of operation, both from a cardiac cause. One had a myocardial infarction and subsequent heart failure after EVAR and the other died from heart failure after OR. Both patients had a preoperative American Society of Anesthesiologists (ASA) classification of III. There was no difference in the overall or cardiac mortality rate between the two study groups (*Table 5*).

Myocardial infarction occurred in three patients, one of whom died. Congestive heart failure was encountered in three patients, two of whom died. The incidence of combined clinical cardiac complications (including cardiac death, myocardial infarction and congestive heart failure) was 5 per cent (three of 57 patients) after EVAR and 11 per cent (two of 19) after OR; this difference was not significant.

Table 5 Outcome events in the two study groups

	EVAR (*n* = 57)	OR (*n* = 19)	*P*§
Death (both cardiac)	1 of 57 (2)	1 of 19 (5)	0·4
Myocardial infarction	2 of 57 (4)	1 of 19 (5)	1·0
Congestive heart failure	2 of 57 (4)	1 of 19 (5)	1·0
Combined clinical cardiac outcome events*	3 of 57 (5)	2 of 19 (11)	0·6
ST abnormality	10 of 57 (18)	8 of 19 (42)	0·06
Wall motion abnormality on TEE†	7 of 55 (13)	5 of 18 (28)	0·16
Myocardial ischaemia‡	15 of 57 (26)	10 of 19 (53)	0·05

Values in parentheses are percentages. *Including all cardiac deaths, myocardial infarctions and episodes of heart failure. †Transoesophageal echocardiography (TEE) data missing for three patients owing to failure to introduce probe (one patient), logistic reasons (one) and urgent repair because of rupture (one). ‡Detected by electrocardiography or TEE. §χ^2 test. EVAR, endovascular repair of abdominal aortic aneurysm (AAA); OR, open AAA repair

Physiological cardiac assessment

ST elevation or depression occurred after operation in 18 patients (24 per cent of observations). Wall motion abnormalities of the left ventricular wall was observed during TEE in 12 patients (16 per cent of recorded examinations); seven of these had no ST abnormalities. Signs of myocardial ischaemia on ECG or TEE were present in 25 patients (33 per cent of observations); there was a significantly lower incidence in patients who had EVAR (26 (95 per cent confidence interval 16–40) per cent *versus* 53 (29–76) per cent after OR) (*Table 5*). Myocardial ischaemia was clinically silent in 21 of these 25 patients. In four of five patients with adverse clinical events, myocardial ischaemia had already been detected by physiological cardiac testing.

Discussion

A randomized trial is the most effective study design to ascertain comparability of treatment groups. In a study focusing on the response of the heart during and after endovascular and open AAA repair, various factors need to be considered: previous coronary events, known angina, severity of angina, episodes of congestive heart failure and the presence of occult coronary lesions. In the present study all these factors were carefully recorded. Patients classified as ASA IV, who were considered unfit for OR, were not included and received EVAR. In addition, patients referred from other centres were excluded. As a result, 13 patients underwent EVAR outside the trial during the study period. This policy resulted in patient groups with equally distributed known, and possibly unknown, cardiac and non-cardiac risk factors.

Cardiac complications are the major cause of death after conventional AAA repair; up to 60 per cent of all deaths are cardiac[1–3]. One of the potential advantages of EVAR is that the severity of cardiac stress may be reduced, which could eventually reduce the operative mortality rate. To date, several comparative studies have failed to demonstrate any reduction in cardiac morbidity and mortality rates with EVAR[12–20]. The prevalence of clinical cardiac events – myocardial infarction, congestive heart failure and severe arrhythmia – after elective OR is about 15 per cent[1,21–23], so it is no surprise that these relatively small series failed to demonstrate any differences. Previous studies were not randomized, but contained historical controls with contemporary patients, features that preclude a proper comparison.

One of the premises during planning of the present study was that clinical cardiac complications constitute the tip of an iceberg. Many ischaemic events occur several days after surgery and the majority (up to 90 per cent) are silent[6,24,25]. Sensitive diagnostic methods may allow the identification of more signs of cardiac ischaemia or undue cardiac stress than ECG and clinical observation alone. In previous studies it was demonstrated that segmental wall motion abnormalities, identified using TEE, are more sensitive and earlier indices of myocardial ischaemia than electrocardiographic changes or clinical monitoring alone[26–30]. When using predictive variables for clinical cardiac complications, a randomized comparative series does not need a large number of patients.

The present study compared haemodynamics and the physiological stress of the two procedures on the myocardium. The baseline levels (10 min before clamping) of blood pressure and SWI were higher during OR. These findings may be attributed to a higher level of operative stress during OR as a result of laparotomy and small bowel retraction. In support of this hypothesis are the findings of Thompson and colleagues[15], who demonstrated a significant increase in plasma adrenaline concentration at the start of OR, while no increase was observed during EVAR.

The intraoperative evolution of blood pressure, heart rate and cardiac index during and after aortic occlusion was comparable during the two procedures. The significant decrease in SVR during OR compared with the stable value during EVAR may be explained as follows. During OR, SVR decreased after prolonged cross-clamping as a result of reperfusion of a maximally vasodilated distal vascular bed. The fact that this effect was not observed during EVAR may be attributed to the brief period of aortic occlusion. Conversely, Baxendale *et al.*[20] observed a comparable decrease in SVR after aortic occlusion in both operations. Patients in their study had aortouni-iliac endografts, and both femoral arteries were cross-clamped for over 100 min. This could explain the differences in haemodynamics with respect to the present study, in which second-generation endovascular devices were used and only one limb was clamped briefly (Stentor or Vanguard grafts) or both limbs consecutively (AneuRx or Lifepath). Few other studies have investigated the cardiac response to EVAR relative to OR. A comparison of combined clinical cardiac events (myocardial infarction, congestive heart failure and cardiac death) was recently published by de Virgilio *et al.*[17]. Data following EVAR were collected prospectively, while cardiac complications from the surgical cohort were retrieved retrospectively. Important differences existed with regard to the age, referral pattern and possibly comorbidity between treatment groups. These flaws detracted considerably from their conclusion that there was no difference in clinical cardiac events relative to treatment. Alternatively, Treharne *et al.*[31] observed a significantly lower operative mortality rate after EVAR. The bearings of the latter study, however, are unclear since the control group with open surgery had an unusually high operative mortality rate of 16 per cent.

Another important finding in the present study was that after aortic occlusion the SWI, a direct measure of myocardial performance, decreased significantly during OR but increased during EVAR. This indicates that myocardial performance was less compromised and the repair was better tolerated by the myocardium during EVAR. A possible explanation for these findings is the duration of aortic occlusion. During EVAR, restoration of flow after a brief moment of aortic occlusion may cause a reactive hyperaemia in the legs and lead to an increase in cardiac index and SWI. In contrast, reperfusion of the lower limbs after prolonged cross-clamping during OR induces the release of vasoactive and cardiodepressant mediators from the ischaemic tissues[32].

Operative cardiac risks are influenced by several factors. The extensive preoperative investigations and intraoperative monitoring in this study may have resulted in improved cardiac management. Patients who had OR may have benefited more from this optimization of their cardiac condition than those who had EVAR. Cardiac complications may also be influenced by the type of anaesthesia. All patients in the present study had general anaesthesia. However, EVAR can be performed under local anaesthesia[33,34]. Future studies could investigate the cardiac stress response to EVAR under local anaesthesia.

Perioperative myocardial ischaemia and infarction may also be associated with long-term events. Mangano *et al.*[35] demonstrated that perioperative myocardial ischaemia increased the risk of serious cardiovascular outcomes by a factor of nine for 2 years after non-cardiac surgery. Similarly, McFalls *et al.*[36] noted a 4-year survival rate of nearly 90 per cent after vascular surgery in patients who had an uncomplicated course compared with only 55 per cent in those who had a perioperative myocardial infarction. Clinical studies with longer follow-up are needed to demonstrate any potential extended beneficial effect of EVAR on clinical events and mortality rate.

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Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion

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Background: Macrolide treatment has been reported to lower the risk of recurrent ischaemic heart disease. The influence of macrolides on the expansion rate of abdominal aortic aneurysms (AAAs) remains unknown. The aim was to investigate the effect of roxithromycin on the expansion rate of small AAAs.

Methods: A total of 92 subjects with a small AAA were recruited from two populations. One population consisted of 6339 men aged 65–73 years who were offered a hospital-based mass screening programme for AAA. From this population 66 subjects were recruited. The remaining 26 men were recruited from among 49 subjects diagnosed at interval screening for an initial aortic diameter between 25 and 29 mm. Subjects were randomized to receive either oral roxithromycin 300 mg once daily for 28 days or matching placebo, and followed for a mean of 1·5 years.

Results: The mean annual expansion rate of AAAs was reduced by 43 per cent in the intervention group (1·56 mm per year), compared with 2·75 mm per year following placebo ($P = 0{\cdot}02$). Multiple linear regression analysis showed that roxithromycin treatment and initial AAA size were significantly related to AAA expansion when adjusted for smoking, diastolic blood pressure and immunoglobulin A level of 20 enzyme immunounits or more. Logistic regression analysis confirmed a significant difference in expansion rates above 2 mm annually between the intervention and placebo groups: odds ratio = 0·09 (95 per cent confidence interval 0·01–0·75).

Conclusion: In comparison to placebo, roxithromycin 300 mg daily for 4 weeks reduced the expansion rate of AAAs.

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Introduction

Chlamydia pneumoniae has been demonstrated in atherosclerotic lesions of the coronary arteries, the carotid arteries and in abdominal aortic aneurysms (AAAs) by immunocytochemistry, the polymerase chain reaction (PCR) and electron microscopy[1–5]. Seroepidemiological studies have confirmed an association between *C. pneumoniae*, atherosclerosis and the risk of acute myocardial infarction[6–9]. Furthermore, immunoglobulin (Ig) A antibodies against *C. pneumoniae* at a level of 20 enzyme immunounits (EIU) or greater have been demonstrated to be associated with an increased expansion of small AAAs[10]. These facts, combined with the finding of a variable inflammatory process in the aneurysm wall[11,12] suggestive of infection, provided the rationale for an intervention trial to assess the effect of antichlamydial treatment on the expansion rate of AAAs.

Screening for AAA seems realistic in the future[13,14]; however, most aortic aneurysms are too small to warrant repair when first detected. Currently there are no therapeutic approaches proven to reduce aneurysm expansion. Consequently, if antibiotic therapy could minimize the expansion rate of AAAs it would have an impact on the benefit and cost-effectiveness of screening strategies and the management of small aneurysms. Furthermore, an opportunity to offer a non-surgical treatment of small AAAs might reduce the psychological side-effects of having a small aortic aneurysm detected by screening[15].

The aim of this study was to investigate the effect of roxithromycin on the expansion rate of small AAAs in comparison with placebo, and to assess the impact of this treatment on co-variates associated with the expansion of small abdominal aneurysms.

Patients and methods

Study population

Participants were recruited from two populations. Population A consisted of 6339 randomly selected men aged 65–73 years in Viborg County, Denmark, who in the interval from 1994 to 1998 were offered screening for AAA by abdominal ultrasonography at their regional hospital as part of a population-based screening study. Population B consisted of 377 men in whom an ectatic aorta, defined as infrarenal aortic diameter of 25–29 mm or distal/renal aortic diameter ratio greater than 1·2, was previously detected in population A[16].

Eligible men had an AAA, defined as an infrarenal aortic diameter of 30 mm or more, that was detected by ultrasonography on the day of study entry, and from whom informed consent was obtained (inclusion criteria). The exclusion criteria comprised known or suspected allergy to the trial product or related products, previous participation in the study, inability to comply with the study protocol, current treatment with macrolides or receipt of any macrolide antibiotic in the 3 months before the study. A total of 92 men were included in the study (66 from population A and 26 from population B).

Baseline assessment

Medical history, current medication and smoking habits were recorded. The highest brachial blood pressure and the lowest systolic ankle blood pressure were recorded. A blood sample was taken and serum was stored at −21°C until analysis. A new commercially available enzyme-linked immunosorbent assay (ELISA) from Labsystems, Helsinki, Finland (LOY-EIA) was used to detect antibodies against IgA.

Intervention

Subjects were randomly assigned in a 1 : 1 proportion to receive either oral roxithromycin 300 mg once daily for 28 days or matching placebo. The intervention was initiated on the day of study inclusion. As part of the blinded study design, all eligible men were randomized before any scans were performed. The allocation schedule was carried out with the use of Epi-Info version 6 (www.cdc.gov/epiinfo), and the generator was separated from the executor. Placebo tablets with similar characteristics were used. During the trial the blinding codes were located at the administration office of Viborg Hospital, and were broken only once all follow-up scans had been done and the follow-up information collected.

A doctor and a nurse, specially trained in ultrasonography, alternated between organizing the scans and performing the B-mode imaging. From 1998 the same doctor carried out all the imaging using the same scanner. Consequently, strict standards of measurement were employed using only one scanner and one observer during the trial. The B-mode scans were carried out with a small Phillips SDR 1550 (Phillips, København, Denmark) with linear 4-MHz transducer and calliper light pen. To estimate the intraobserver variation, repeated measurements of the maximal anterior–posterior diameter were carried out in 25 men.

Follow-up

Subjects were followed annually with repeat ultrasonography to assess the size of the aneurysm and to determine the need for surgery, admission to hospital with an atherosclerotic disease, death or any other adverse event. Men with an aortic aneurysm greater than 50 mm were referred for operation.

Outcome measures

The primary outcome measure was the mean change in the anterior–posterior diameter of the aneurysm during observation, transformed to annual units (expansion rate). Secondary outcome measures included the proportion of men referred for surgery, the proportion admitted to hospital with cardiovascular disease, the number of deaths and the number of subjects who experienced other adverse events.

Ethics

The trial was approved by the national board of health and the local scientific ethics committee, and was reported to the data protection authorities.

Statistical analysis

Initial AAA size, smoking, hypertension and *C. pneumoniae* IgA titre of 20 EIU or more have been reported to be related to the expansion rate of abdominal aneurysms. Therefore, subgroup analysis was planned, adjusting the results for these co-variates. Using power calculations it was estimated that approximately 100 subjects were needed to detect a 33 per cent reduction in aneurysm expansion rate, which was considered clinically significant.

The analysis was completed on an intention-to-treat basis. The Statistical Package for the Social Sciences (SPSS) version 10·0 (SPSS, Chicago, Illinois, USA) was used to perform Student's t test, Fisher's exact test, the χ^2 test, and multiple linear and logistic regression analyses.

Results

Baseline characteristics

Of the 6339 men in population A, 4843 attended for screening (76 per cent). Of these, 191 (4 per cent) had an AAA according to the definition (30 mm or greater). Twenty-four of the 191 men had an AAA above 5 cm in diameter at the time of screening and were referred for surgery. The remaining 167 subjects were offered annual follow-up imaging to assess aneurysm expansion. Over a 3-year interval from 1995 to 1998 a further 48 men were referred for operation and 19 died, leaving 100 eligible subjects for the study[14]. Of these 100 men, informed consent was obtained from 66, who entered the trial. From population B, 49 of the aortas that were initially ectatic (25–29 mm) expanded to fulfil the inclusion criteria of the study (greater than 30 mm); informed consent was obtained from 26 (53 per cent) of these 49 men. Thus, a total of 92 men entered the trial (*Fig. 1*). All the eligible men were randomized before any scans were carried out, as part of the blinded study design. Consequently, eight men were withdrawn immediately because the control scan showed that the diameter of the aneurysm was greater than 5 cm, and they were referred for surgery. Of the remaining 84 small aneurysms, 31 were 3·0–3·4 cm in diameter, 24 were 3·5–3·9 cm, 17 were 4·0–4·4 cm and 12 were 4·5–4·9 cm. The mean(s.d.) size of these aneurysms was 37·5(5·4) mm.

During the first year of observation, three subjects died and five were lost to follow-up, leaving 76 men eligible for control scan. In the second year a further five men were referred for surgery, two died and four were lost to follow-up, leaving 63 subjects eligible. All participants were randomized over a 1-year interval, and the duration of observation varied from 10 months to 2·2 years (mean 1·5 years). Because the same observer carried out all the scans, a few subjects were imaged within 1 year, for practical reasons.

There was no significant difference between the two study groups with regard to demographics and previously reported risk factors for expansion (*Table 1*)[17–21].

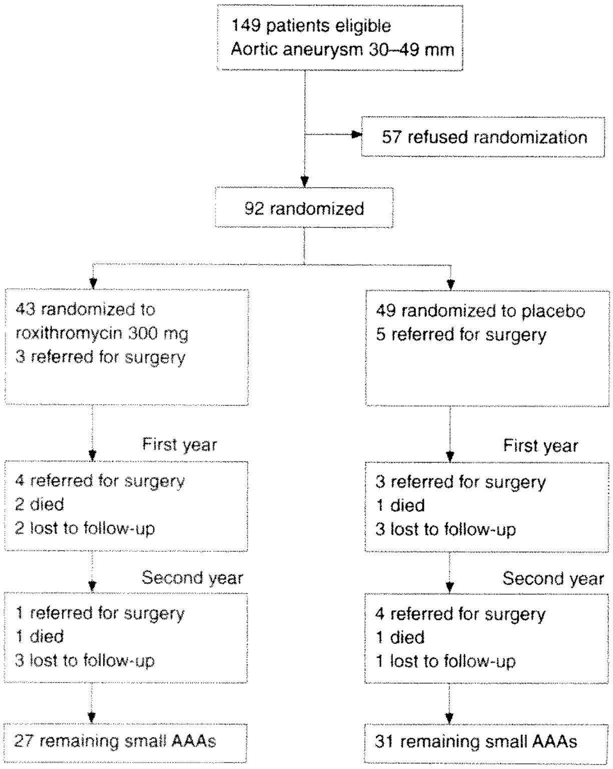

Fig. 1 Trial profile. AAA, abdominal aortic aneurysm

Table 1 Demographic and expected risk factors for abdominal aortic aneurysm expansion

	Intervention group	Placebo group	*P*
After randomization			
No. of subjects	43	49	
Age (years)*	72(3·7)	73(3·7)	0·35
AAA size (mm)			
Mean(s.d.)	38·1(5·7)	36·9(5·1)	0·33
3·0–3·4	15	16	0·86
3·5–3·9	11	13	0·81
4·0–4·4	8	9	1·00
4·5–4·9	8	4	0·35
Diastolic blood pressure (mmHg)*	86·5(13·1)	85·5(12·8)	0·85
ABPI*	0·9(19·5)	0·9(19·0)	0·85
Smoker (yes = 1, no = 0)*	0·6(0·4)	0·6(0·5)	0·76
Chlamydia pneumoniae IgA*			
Mean(s.d.)	18·5(19·1)	18·7(12·5)	0·41
Titre ⩾ 20	22·5(22·9)	23·8(14·1)	0·43
At 1-year follow-up			
AAA size (mm)*	39·9(6·7)	39·6(6·5)	0·98
Diastolic blood pressure (mmHg)*	86·8(13·0)	85·7(9·3)	0·63
ABPI*	0·9(0·2)	0·9(0·2)	0·31
C. pneumoniae IgA*			
Mean(s.d.) EIU	26·7(20·1)	30·2(20·1)	0·33
Titre ⩾ 20 EIU	28·5(22·9)	32·7(14·1)	0·43
At 2-year follow-up			
AAA size (mm)*	39·1(5·7)	40·1(7·5)	0·73
Diastolic blood pressure (mmHg)*	88·6(13·9)	87·8(10·3)	0·76
ABPI*	0·9(22·8)	1·0(31·4)	0·31

*Values are mean(s.d.). AAA, abdominal aortic aneurysm; ABPI, ankle : brachial pressure index; Ig, immunoglobulin; EIU, enzyme immunounits. Student's t test

Drop outs and side-effects

No participant stopped the medication because of side-effects and no adverse events were noted. Five subjects (12 per cent) from the intervention group and four (8 per cent) from the placebo group were lost to follow-up (*Fig. 1*). Two subjects were lost because they moved to another part of the country and three moved abroad. Two did not want any further follow-up because of co-morbidity. The reasons for loss of the final two subjects are unknown. Four men required hospital admission for acute myocardial infarction; all were in the placebo group.

Table 2 Mean annual expansion for abdominal aortic aneurysms in the intervention and placebo groups during follow-up

	First year			Second year			Overall observation period			
	Macrolide	Placebo	*P*†	Macrolide	Placebo	*P*†	Macrolide	Placebo	*P*†	OR‡
Expansion rate (mm per annum)										
All AAAs	1·56	2·80	0·02	2·06	2·16	0·64	1·56	2·75	0·02	
AAA < 36·5 mm	1·34	2·34	0·16	2·08	0·45	0·17	1·34	2·28	0·16	
AAA ⩾ 36·5 mm	1·76	3·31	0·08	2·03	3·19	0·53	1·76	3·27	0·08	
IgA titre < 20 EIU	1·64	2·52	0·08	1·80	1·13	0·31	1·64	2·47	0·08	
IgA titre ⩾ 20 EIU	1·12	3·84	0·19	2·57	3·49	0·77	1·12	3·70	0·15	
No. of patients										
Size ⩾ 36·5 mm	23	20		23	27		24	24		2·33 (0·46–15·43)
IgA titre ⩾ 20	8	9		—	—		14	18		0·78 (0·24–2·49)
Expansion rate > 2 mm per year	14	22		6	11		14	23		0·37 (0·11–1·29)
Referred for surgery*	4	3		1	4		5	7		0·79 (0·18–3·18)
Acute myocardial infarction	0	1		0	3		0	4		—
Lost to follow-up	2	3		3	1		5	4		1·48 (0·29–7·98)
Dead	2	1		1	1		3	2		1·76 (0·19–21·95)

*Abdominal aortic aneurysm (AAA) size greater than 50 mm. Ig, immunoglobulin; EIU, enzyme immunounits. †‡Odds ratio (OR) with 95 per cent confidence interval in parentheses. Student's *t* test, Fisher's exact test

Table 3 Roxithromycin treatment and predictors of expansion for small aneurysms using linear regression analysis.

	Expansion rate (mm per annum)		
	First year	Second year	Whole study interval
AAA size, mm	0·16 (0·04 to 0·27)	0·23 (0·05 to 0·42)	0·16 (0·04 to 0·27)
Roxithromycin	– 1·91 (– 3·18 to 0·65)	– 0·43 (– 2·31 to 1·45)	– 1·92 (– 3·19 to 0·64)
Diastolic blood pressure, mmHg	– 0·02 (– 0·07 to 0·03)	– 0·06 (– 0·13 to 0·01)	– 0·02 (– 0·07 to 0·03)
IgA antibodies, all levels	0·02 (– 0·02 to 0·05)	0·00 (– 0·51 to 0·05)	0·01 (– 0·02 to 0·03)
Smoker*	0·87 (– 0·44 to 2·19)	1·68 (– 0·41 to 3·77)	0·88 (– 0·44 to 2·20)
Median AAA < 36·5 mm	0·32 (– 0·07 to 0·70)	0·01 (– 0·81 to 0·83)	0·32 (– 0·07 to 0·71)
Roxithromycin	– 1·57 (– 3·12 to 0·02)	1·07 (– 2·28 to 1·58)	– 1·58 (– 3·12 to 0·02)
Diastolic blood pressure, mmHg	– 0·05 (– 0·11 to 0·01)	0·00 (– 0·81 to 0·83)	– 0·05 (– 0·11 to 0·01)
IgA antibodies, all levels	0·07 (– 0·11 to 0·12)	– 1·46 (– 1·23 to 0·10)	0·07 (– 0·11 to 0·01)
Smoker*	0·35 (– 1·63 to 2·34)	2·15 (– 2·15 to 6·45)	0·35 (– 1·63 to 2·34)
Median AAA ⩾ 36·5 mm	0·34 (0·10 to 0·57)	0·37 (– 0·17 to 0·90)	0·34 (0·10 to 0·57)
Roxithromycin	– 2·64 (– 4·41 to 0·92)	– 0·99 (– 4·31 to 2·35)	– 2·64 (– 4·41 to 0·92)
Diastolic blood pressure, mmHg	– 0·02 (– 0·08 to 0·04)	– 0·01 (– 0·23 to 0·03)	– 0·02 (– 0·08 to 0·04)
IgA antibodies, all levels	0·00 (– 0·05 to 0·04)	0·00 (– 0·08 to 0·03)	0·00 (– 0·05 to 0·04)
Smoker*	0·68 (– 1·03 to 2·40)	2·49 (– 1·38 to 6·36)	0·68 (– 1·03 to 2·40)
Initial IgA level ⩾ 20 EIU (*n* = 17)	0·00 (– 0·11 to 0·11)	– 0·02 (– 0·10 to 0·06)	0·00 (– 0·11 to 0·11)
AAA size, mm	– 0·18 (– 0·84 to 0·49)	0·00 (– 0·37 to 0·78)	– 0·18 (– 0·84 to 0·49)
Roxithromycin	– 0·31 (– 4·30 to 3·68)	0·22 (– 4·43 to 2·48)	– 0·31 (– 4·30 to 3·68)
Diastolic blood pressure, mmHg	– 0·10 (– 0·24 to 0·04)	– 0·09 (– 0·19 to 0·02)	– 0·10 (– 0·24 to 0·04)
Smoker*	0·02 (– 5·90 to 5·87)	0·17 (– 4·51 to 4·99)	0·02 (– 5·90 to 5·88)

Values in parentheses are 95 per cent confidence intervals. *Yes = 1, no = 0. AAA, abdominal aortic aneurysm; Ig, immunoglobulin; EIU, enzyme immunounits

Table 4 Crude and adjusted odds ratios using annual expansion of abdominal aortic aneurysm below or above 2 mm as the dependent variable, adjusting for expansion risk factors used in *Table 3*, and treatment with macrolide *versus* placebo

	Crude odds ratio	Adjusted odds ratio
Roxithromycin	0·30 (0·07–1·19)	0·09 (0·01–0·75)
AAA size, mm	1·15 (1·04–1·32)	1·32 (1·06–1·64)
Diastolic blood pressure, mmHg	0·98 (0·93–1·03)	0·97 (0·91–1·04)
Initial IgA level	1·02 (0·91–1·06)	1·03 (0·98–1·08)
Smoker (yes = 1, no = 0)	4·17 (0·84–20·79)	7·71 (0·93–63·70)

Values in parentheses are 95 per cent confidence intervals. AAA, abdominal aortic aneurysm; Ig, immunoglobulin

Five subjects from the intervention group and seven from the placebo group were referred for surgery during follow-up because the aneurysm reached 50 mm in diameter (odds ratio (OR) 0·79 (95 per cent confidence interval (c.i.) 0·18–3·18)). Three subjects (7 per cent) in the intervention group died, and two (4 per cent) in the placebo group.

Aneurysm expansion

During the observation, the overall mean expansion rate for all AAAs in the intervention group was reduced by 43 per cent: 1·56 mm per year compared with 2·75 mm per year in the placebo group ($P = 0{\cdot}02$). For the first year of follow-up the mean annual expansion rate of aortic aneurysms was reduced by 44 per cent in the intervention group: 1·56 *versus* 2·80 mm per year in the placebo group ($P = 0{\cdot}02$). During the second year of follow-up the reduction was only 5 per cent in the intervention group: 2·06 *versus* 2·16 mm per year in the placebo group ($P = 0{\cdot}64$) (*Table 2*).

There was a trend towards an increased effect of roxithromycin in men with an AAA above the median initial size (36·5 mm) and also in those with an initial IgA titre of 20 EIU or more (*Table 2*). Mean IgA levels were 12 per cent lower in the intervention group than in the placebo group after 1 year, although this was not significant ($P = 0{\cdot}67$). Further analysis did not reveal any differences between AAA expansion and IgA level.

Multiple linear regression analysis with the mean annual expansion rate as the dependent variable, and adjusted for variables reported to influence AAA expansion, is shown in *Table 3*. Initial aneurysm size and macrolide treatment, and AAA diameter above or equal to the median (36·5 mm) remained significantly related to aneurysm expansion in the first year, and through the whole observation period. Initial diastolic blood pressure and IgA level of 20 EIU or more had no influence on the expansion in this analysis.

Because 95 per cent of the repeated ultrasonographic measurements were within a 2-mm variation (s.d. 0·83), logistic regression analyses were conducted using annual expansion rates below or above 2 mm as the dependent variable, adjusting for the same risk factors as in the multiple linear regression analysis (*Table 4*). The adjusted logistic analysis confirmed a significant difference in expansion between the intervention and placebo groups: OR 0·09 (95 per cent c.i. 0·01–0·75). Initial AAA size remained a risk factor for expansion above 2 mm per year, with an adjusted OR of 1·32.

Fourteen aneurysms from men in the intervention group and 23 from the placebo group expanded more than 2 mm per year during the observation period. However, this difference was not significant (OR 0·37 (95 per cent c.i. 0·11–1·29)). This may be due to the difference in the number of larger AAAs in the two groups (*Table 1*). Adjusting for this, the adjusted OR became significant: OR 0·28 (0·10–0·80).

Discussion

Compared with placebo, once-daily administration of roxithromycin 300 mg reduced the expansion rate of small AAAs. The benefit was time dependent, being greatest during the first year of follow-up. Roxithromycin might be more effective in patients with a larger initial AAA size and a *C. pneumoniae* titre of 20 EIU or more.

The strength of this study is the recruitment of patients through population-based screening and the randomized placebo-controlled blinded study design. There was no evidence of selection bias between the two groups, indicated by identical baseline characteristics. Few patients were lost to follow-up, making attrition bias unlikely. Finally, the potential detection bias was also low, based on the intraobserver data from this study, where validation of the measurements showed an intraobserver variation of 2 mm, similar to that of other studies[22,23].

The major weakness was the limited number of patients studied. The impact of macrolides on other major clinical outcomes, such as the need for AAA surgery and death, could not be assessed in this study. Also, no measures to monitor potential environmental effects of the use of macrolides were included.

Roxithromycin reduced the mean annual aneurysm expansion rate by 44 per cent in the first year, but by only 5 per cent in the second year of follow-up. A time-dependent effect of macrolides has also been observed in other studies. In the study by Gurfinkel *et al.*[24] an effect was observed after 30 days of follow-up, but not after 180 days. Gupta *et al.*[25] found an effect after 30 days, but follow-up was not extended. Anderson *et al.*[26] first observed patients after 180 days, and at this time no effect was seen. The fact that the effect of macrolides seems to be time limited supports a true protective effect on expansion. It also raises the question of whether a repeat course should be given. Gieffers *et al.*[27] have recently demonstrated that *C. pneumoniae* uses monocytes as a transport system for systemic dissemination and enters a persistent state not covered by antichlamydial treatment. This might explain the time-dependent effect as circulating monocytes are reinfected.

Two of the above-mentioned studies used azithromycin; one used roxithromycin. So far, there are no recommendations or guidelines regarding the drug of choice and for how long it should be given. Roxithromycin was used here because it is known to have fewer gastrointestinal side-effects and is cheaper than azithromycin. Administration for 28 days is the general recommendation from the Danish National Board of Medicine Administration concerning complicated chlamydial infections.

The mean annual expansion rate of AAAs under 5 cm in diameter is reported to be about 3 mm per year[28]. All expansion rates in the intervention group were below this level. The placebo group had a similar expansion rate to that in these earlier studies. The highest mean annual expansion was noticed in men from the placebo group with an initial IgA level above or equal to 20 EIU and an AAA size above the median value. Intervention with roxithromycin also had the greatest impact on the expansion of these aneurysms. However, the effect of an IgA level above or equal to 20 EIU could not be confirmed by regression analysis. More subjects in the placebo group were referred for operation, although this was not significant: OR 0·79 (95 per cent c.i. 0·18–3·18).

Chlamydial serology is lacking in well defined standards. The ELISA used allows detection of the various immunoglobulin types against *C. pneumoniae*[10]. IgA antibody titres usually decline and disappear 3–12 months after infection and a persistently raised level of IgA is indicative of chronic infection. IgG antibodies may persist for some years and a fourfold increase in IgG titre, or IgM titre of 32 EIU or more, approximately 3 weeks after onset indicates acute infection[29,30].

C. pneumoniae IgG titres of 128 EIU or more are believed to indicate past or pre-existing infection, but persistence of the short-lived IgA may be a better marker of chronic infection than IgG. An IgA level greater than or equal to 20 EIU was used here because in an earlier study this was demonstrated to be a significant independent predictor of AAA expansion[10]. The mean IgA level 1 year after macrolide treatment was 12 per cent lower than that in the placebo group. This, however, was not statistically significant and a reduction in expansion rates was noticed in all aneurysms. Determination of initial IgA levels is not a suitable method of detecting a subgroup of patients with aneurysms who might benefit from macrolide treatment.

The present study has not assessed the mechanism of action of the macrolide. It is still not proven that *C. pneumoniae* causes aortic aneurysms or promotes their expansion. Macrolides in general do possess anti-inflammatory properties, and act on other bacteria as well, either of which may explain the protective effect on AAA found in this study. It is important to investigate the relationship between *C. pneumoniae* and AAA further, as vaccination may be a future option. The findings in this study suggest some role for *C. pneumoniae* because the effect of roxithromycin seemed to be greater in patients with high antibody levels, and the antibody titre fell more in the macrolide group.

Macrolide treatment had a significant effect on small AAA growth rates, and could be considered in patients unfit for operation. Further intervention trials should be performed on a larger scale to confirm the present results; the studies should include harder endpoints, such as the need for AAA surgery. Studies should also assess the impact that macrolide antibiotics may have on the environment.

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Original article

Non-operative management of haemobilia

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Background: The aim was to evaluate a non-operative approach to the management of haemobilia.
Methods: This was a retrospective analysis of patients presenting over 10 years with haemobilia. All patients had upper gastrointestinal endoscopy, abdominal ultrasonography and digital subtraction angiography. Superselective coil and/or Gelfoam embolization was done as close as possible to the bleeding site. Completion angiography was performed routinely to confirm adequate embolization.
Results: There were 23 patients with liver trauma and six with inflammatory conditions. All patients required resuscitation with fluids and blood transfusion, and had the haemobilia controlled successfully by angiographic embolization. There was one death from fulminant hepatic sepsis.
Conclusion: This series attests to the efficacy of a non-operative approach to haemobilia using radiological diagnosis and intervention.

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Introduction

Francis Glisson introduced the diagnosis of haemobilia in 1654, but Antoine Portal reported the first documented case in 1777[1]. In 1871 Quincke described the cardinal features of the condition, namely gastrointestinal haemorrhage, biliary colic and jaundice. The advent of more sophisticated imaging techniques has culminated in an increased frequency of diagnosis of haemobilia and the potential for its successful management. Optimum therapy remains uncertain because of the small numbers in reported series. While interventional radiological and percutaneous hepatobiliary procedures account for the majority of reported cases in the literature today, trauma and, to a lesser extent, hepatic infection and infestations remain leading aetiological agents in Third World environments[2,3].

Therapeutic options for the management of this condition revolve around surgery[4,5] and interventional radiology. This paper evaluates an experience of a non-operative approach to the management of haemobilia.

Patients and methods

Over 10 years from June 1990 to June 2000, 29 patients with haemobilia presenting to the surgical services at King Edward VIII Hospital in Durban, South Africa were evaluated. There were 28 men. All 29 patients were young and healthy; their mean age was 22 (range 14–40) years.

All patients had blood investigations performed including a full blood count, measurement of urea and electrolytes, partial thromboplastin and prothrombin times, and a liver function profile. All patients had upper gastrointestinal endoscopy, abdominal ultrasonography and, in the presence of persistent upper gastrointestinal haemorrhage, coeliac digital subtraction angiography. Coeliac angiography was performed via femoral artery access using the Seldinger technique. All patients had superselective coil and/or gelfoam (Spongostan®, Johnson and Johnson, Durban, South Africa) embolization as close as possible to the bleeding site to reduce the risk of significant hepatic necrosis. A 5-Fr catheter system sufficed in the majority of cases; a 2·5-Fr microcatheter with coaxial delivery was required on three occasions. Completion angiography was performed routinely to confirm adequate embolization. Once the melaena had stopped and the haemoglobin level was maintained, patients were discharged at least 72 h after radiological intervention.

All patients were followed at 2 weeks, 1 month and then 3-month intervals for 1 year after intervention.

Results

In 23 patients there was a preceding history of abdominal trauma that was managed by laparotomy. Twenty patients had penetrating abdominal trauma: 16 had sustained a gunshot wound and four had stab wounds. Three patients

Table 1 Mechanism and management of hepatic injury

Mechanism of injury	*n*	Drain	Debride and suture	Packs
Gunshot	16	7	6	3
Stab	4	2	1	1
Blunt trauma	3	2	1	–

All hepatic injuries were drained

sustained blunt abdominal trauma following a motor vehicle collision. *Table 1* demonstrates the mechanisms of injury and the management undertaken at operation. The right lobe of the liver was involved in all but two patients. Seven patients had an isolated hepatic injury; other patients had associated injuries to the stomach ($n = 6$), duodenum ($n = 1$), small bowel ($n = 5$) and colon ($n = 6$).

Of six patients who developed haemobilia without a preceding history of hepatic trauma, four had complicated biliary ascariasis, three of whom had previously required surgery for the condition. One patient had complicated peptic ulcer disease and the sixth required drainage of a localized abscess following open cholecystectomy.

Presentation

The earliest presentation was 7 days after surgery (mean 16 (range 7–211) days). All patients were readmitted for this problem after apparent recovery from the preceding surgical procedure. Anaemia with melaena was observed in all patients; haematemesis was noted in only three. Colicky right upper quadrant pain was present in 15 of the 29 patients, but only 11 were jaundiced.

Management

All patients presented with upper gastrointestinal haemorrhage requiring aggressive resuscitation with crystalloids and blood transfusion. Seven patients with preceding hepatic trauma presented in shock. The mean haemoglobin concentration was 6·1 (range 4–8) g/dl. A mean of 4 (range 2–10) units of packed cells was transfused.

The liver function profiles demonstrated a moderate increase in alkaline phosphatase (mean 270 (range 190–510) IU; normal up to 150 IU) and mild increases in bilirubin level (mean 32 (range 26–81) μmol/l; normal up to 17 μmol/l). The level of aspartate aminotransferase was also marginally increased (mean 34 (range 22–42) IU; normal up to 27 IU). This was similar in both trauma-related and unrelated pathology.

Initial diagnostic investigation in all patients comprised upper gastrointestinal endoscopy as well as abdominal ultrasonography. The latter was performed to identify solid visceral pathology that may have indicated the source of bleeding. The endoscopic examination was normal in 22 patients. In seven patients blood was identified in the second part of the duodenum and in one patient an extrinsic pulsatile mass was identified over the duodenum but the source of haemorrhage could not be defined. Abdominal ultrasonography proved useful in only seven patients; three with ascariasis were identified as harbouring worm nests and in two patients an intrahepatic haematoma was identified. Colour Doppler ultrasonography suggested the diagnosis of intrahepatic false aneurysm and arteriovenous fistula in one patient each (*Fig. 1*).

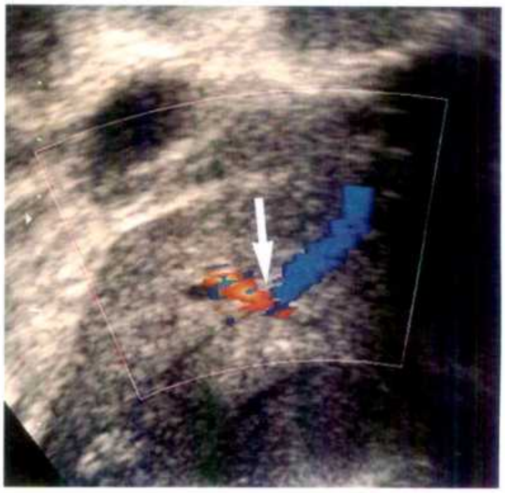
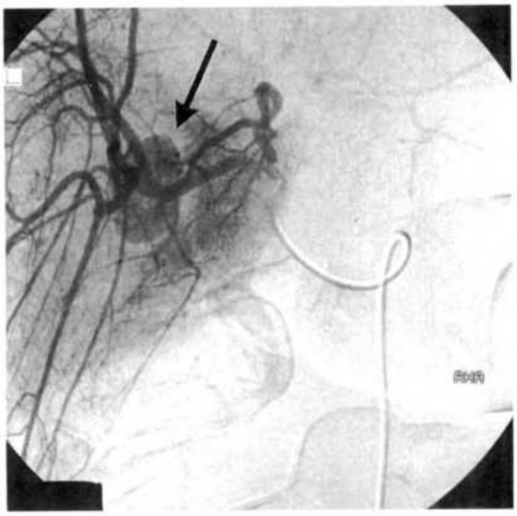


Fig. 1 Longitudinal colour Doppler sonogram demonstrating arteriovenous fistula (arrow)

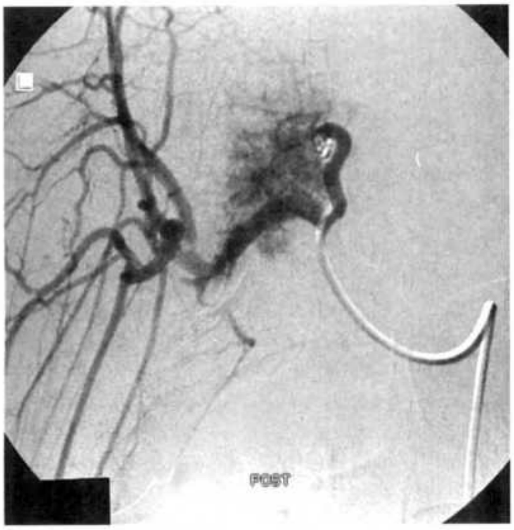
All 29 patients underwent angiography at which a pseudoaneurysm of either the right or left hepatic artery, or a branch thereof, was identified and embolized (*Fig. 2*). In four patients an associated arteriovenous fistula was detected. In one patient, following a gunshot injury to the right lobe of the liver and the duodenum, a hepaticoduodenal fistula was found.

Complications

There were no complications related to the angiographic procedure; in particular, no bleeding from the puncture site or renal impairment was seen. There was one death in this series of 29 patients. This patient, who had undergone laparotomy for a gunshot injury to the liver, required relaparotomy for sepsis that developed 3 days after successful angiographic embolization. He was found to have fulminant hepatic sepsis and necrosis, and died during the reoperation from intractable bleeding consequent to debridement and a refractory coagulopathy.



a Pseudoaneurysm



b After embolization

Fig. 2 Selective right hepatic arteriograms demonstrating a pseudoaneurysm (arrow) (**a**) that was successfully obliterated with the use of a Gianturco® (Eastcoast Medical, Denver, Colorado, USA) embolization coil (**b**)

The remaining patients had an uneventful postprocedural course and remained well during follow-up. All patients were able to return to work within 2 weeks of successful angiographic embolization. At 6-month follow-up, all 28 patients were in good health with no recurrent bleeding. This outcome was maintained in the 18 patients reviewed after 1 year. Ten patients were lost to follow-up.

Discussion

Haemobilia is one of the more commonly reported causes of obscure gastrointestinal haemorrhage. This is particularly so in the current era when interventional radiological and percutaneous procedures are increasingly being undertaken to treat or evaluate hepatobiliary disorders and the transplanted liver[6,7]. The increasing prevalence of abdominal trauma following motor vehicle collisions and interpersonal violence predisposes the liver to trauma that may complicate acutely or belatedly as haemobilia[8]. The diagnosis of haemobilia requires clinical suspicion in the appropriate clinical situation, that is gastrointestinal bleeding without a demonstrable intestinal source in the presence of hepatic pathology.

Failure to identify the source of upper gastrointestinal haemorrhage at endoscopy results in a clinical dilemma. The authors' policy has been to perform abdominal ultrasonography to image the liver and the pancreas in order to identify lesions that may bleed into the duodenum. This is particularly pertinent for hepatic conditions that primarily or secondarily predispose to suppuration. In the tropics, biliary ascariasis complicated by a hepatic abscess may be an important cause of haemobilia. This was noted in four patients in the present series.

The origins of haemobilia may be diverse and include the cystic artery, anomalous hepatic artery, and hepatic artery to portal vein fistulas[9,10]. The advent of laparoscopic surgery has seen the emergence of cystic artery aneurysms presenting with haemobilia. This complication must be considered in patients presenting with upper gastrointestinal bleeding following laparoscopic cholecystectomy[11].

Colour Doppler ultrasonography proved diagnostic in the two patients in whom it was undertaken. The value of duplex sonography is largely operator dependent, and remains to be validated as it offers low sensitivity for smaller lesions and there is no potential for therapeutic intervention.

Following ultrasonography, the best diagnostic option, in the authors' experience, is angiography rather than computed tomography (CT). While the role of CT in assessing the extent of hepatic trauma is universally established, its role in the management of haemobilia is less clear. The currently available helical CT enables identification of parenchymal and associated vascular injuries, such as a false aneurysm, which allows subsequent angiography to be targeted. In the present study CT was used to confirm haemobilia only in patients with suspected hepatic trauma who had not undergone laparotomy. Angiography has the capability of therapeutic intervention; it is attractive because vascular disruption can be identified, the pathology of smaller vessels can be defined precisely, and definitive therapy by radiological intervention may be undertaken following diagnosis.

The embolization technique undertaken in this series did not occlude the artery distal to the aneurysm, yet this approach was consistently successful. The risk of persistent bleeding from collateral vessels following proximal embolization has to be weighed against the possibility of hepatic necrosis when the embolization is done distally as well.

Upper gastrointestinal haemorrhage, jaundice and biliary colic are the triad of symptoms that have been described in surgical texts. The colicky pain associated with haemobilia has been attributed to clot formation in the biliary tree[12]. However, this is controversial as it has been suggested that substances in bile preclude the development of thrombosis[13]. The colicky pain in haemobilia may be due to the sustained distension of the biliary tree by free-flowing blood. This suggests that the symptom would occur only when there is active haemorrhage at the time of presentation. The absence of recognizable pathology at upper gastrointestinal endoscopy and ultrasonography should prompt the use of angiography to localize the source of bleeding if it is clinically significant.

In this series, hepatic artery pseudoaneurysm was the commonest angiographic explanation for haemobilia. Bleeding from pseudoaneurysms is invariably directed into the adjacent disrupted biliary radicle rather than into portal vein radicals. The reasons for this are unclear. It may be a consequence of a pressure gradient, or due to the direction of flow. With respect to arteriovenous fistulas, the liver anatomy favours the development of hepatic artery to portal vein fistulas[14,15]. Communication between the hepatic artery and the hepatic vein consequent to pseudoaneurysm may occur with centrally located lesions, probably owing to the larger-calibre central hepatic veins.

This review attests to the value of a non-operative approach to the management of haemobilia by means of interventional radiological therapy. This approach was invariably beneficial and had an impressive therapeutic success rate coupled with a negligible morbidity and mortality rate. Surgery could be reserved for patients who cannot be managed radiologically.

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Original article

Experience with laparoscopic ultrasonography for defining tumour resectability in carcinoma of the pancreatic head and periampullary region

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Background: Computed tomography (CT) is currently the most widely available staging investigation for pancreatic tumours. However, the accuracy of CT for determining tumour resectability is variable and can be poor. Laparoscopic ultrasonography (LUS) is potentially a more accurate method for disease staging. The authors' experience of LUS for staging carcinoma of the pancreatic head and periampullary region is described.

Methods: Fifty-one patients with potentially resectable pancreatic tumours defined at CT underwent further investigation with LUS. Twenty-seven patients subsequently had an open laparotomy. The evaluations of tumour resectability at CT and LUS were compared with the operative findings.

Results: At LUS, 24 patients were considered to have resectable tumours, 21 non-resectable tumours and six patients were shown to have no pancreatic tumour mass. Twenty-two patients deemed to have a resectable tumour at LUS underwent surgery. Twenty patients were confirmed to have resectable disease and two patients had non-resectable disease. A further five patients underwent surgery. In all five the ultrasonographic diagnosis was confirmed at surgery (four patients with non-resectable disease and no pancreatic tumour in one patient). LUS prevented unnecessary extensive surgery in 53 per cent of patients. For the 22 patients who underwent surgery for potentially resectable disease, the positive predictive value of LUS for defining tumour resectability was 91 per cent.

Conclusion: LUS is an accurate additional investigation for defining tumour resectability and directing management in patients with potentially resectable carcinoma of the pancreatic head or periampullary region.

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Introduction

Carcinoma of the pancreas is the fifth commonest cause of cancer death in the Western world. The diagnosis carries a poor prognosis, with a 1-year mortality rate of greater than 80 per cent[1,2]. Despite this outlook, it is important to identify patients with potentially resectable disease. For such patients, 5-year survival rates of 15–25 per cent for pancreatic and 21–38 per cent for ampullary carcinoma have been reported following operation[3–5]. For patients with non-resectable disease, a variety of palliative procedures can be performed, which reduces the need for unnecessary laparotomy and extensive surgery.

To date, dynamic contrast-enhanced computed tomography (CT) has been the preoperative imaging modality of choice. However, the sensitivity and positive predictive value of CT in defining resectability are only 75 and 38 per cent respectively[6], although there has been some improvement with the use of helical CT[7]. Improvements in assessing resectability have been made by performing preoperative laparoscopic staging to identify small hepatic and peritoneal metastases that are not seen at CT. In these studies, 24–40 per cent of patients deemed to have resectable disease at CT have been demonstrated to have metastatic disease at laparoscopy[8–10]. A refinement of this technique is to use laparoscopic ultrasonography (LUS) in conjunction with direct laparoscopic visualization. Several studies have now demonstrated that LUS improves the accuracy of pancreatic carcinoma staging over laparoscopy alone, providing additional surgical information in 14–25 per cent[11–15]. LUS enables an assessment of liver metastases, deep regional nodal spread and local vascular invasion, which cannot be assessed easily by visualization alone[16,17].

In this paper the authors' experience of LUS in the preoperative assessment of 51 consecutive patients with potentially resectable carcinoma of the pancreatic head or periampullary region is presented.

Patients and methods

Between July 1996 and March 2000, 51 consecutive patients with a diagnosis of potentially resectable carcinoma of the pancreatic head or periampullary region at CT underwent further staging with LUS. All subjects gave informed consent.

For patients presenting with obstructive jaundice the policy was to place an endoscopic stent to provide symptomatic relief. While the jaundice resolved, staging investigations were performed to assess tumour resectability (*Fig. 1*). If the tumour was found to be non-resectable no further operative intervention was planned.

Computed tomography

For 40 patients a single CT imaging protocol was used. Imaging was performed with a CT PACE scanner (GE Medical Systems, Milwaukee, Wisconsin, USA). Patients were starved for 6 h before imaging. Oral contrast (1000 ml 2 per cent Gastrografin; Schering, Berlin, Germany) was administered 1 h before imaging. Axial, precontrast images were acquired from the diaphragm to the third part of duodenum (10 mm slice thickness (SLT), 10 mm gap). Intravascular contrast (Iohexol 350 mg/ml; Nycomed Imaging, Oslo, Norway) was administered in two phases, 70 ml at 2 ml/s followed by 80 ml at 0·6 ml/s. Postcontrast images were acquired after administration of the first 70 ml of contrast (third part of duodenum to top of pancreas: 5 mm SLT, 5 mm gap; top of pancreas to diaphragm: 10 mm SLT, 10 mm gap).

For the remaining 11 patients a variety of scanning techniques and equipment was used by the referring hospital.

Laparoscopic ultrasonography

LUS was performed under general anaesthetic with a surgeon (J.McK.M., *n* = 51) and radiologist (S.A.R., *n* = 45; other radiologists, *n* = 6) present. The images were acquired using a 6·5-MHz Convex Array Transducer Type 8555 with a Medical Ultrasound Scanner Type 2002 (B & K Medical, Gentofte, Denmark). Two disposable 10-mm laparoscopic cannulas were inserted at the umbilicus and in the right upper quadrant just inferior to the costal margin in the mid-axillary line. A 10-mm laparoscope was inserted via one of the ports and the LUS transducer was inserted under direct vision via the other port. Ultrasonographic images were acquired of the liver, biliary tree, duodenum, pancreas and adjacent retroperitoneum. The probe was inserted via both laparoscopic ports to ensure visualization of the pancreas in two planes. A Doppler mode was available on the ultrasound probe. This was of particular use for distinguishing between vessels and dilated pancreatic duct. All LUS was performed without complication.

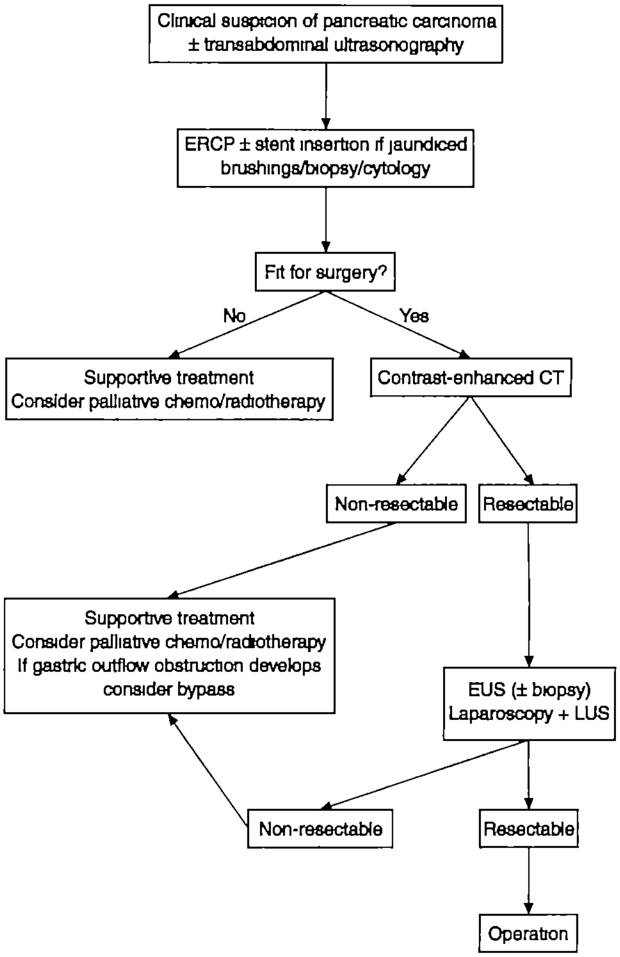

Clinical suspicion of pancreatic carcinoma
± transabdominal ultrasonography
ERCP ± stent insertion if jaundiced
brushings/biopsy/cytology
Fit for surgery?
No
Yes
Supportive treatment
Consider palliative chemo/radiotherapy
Contrast-enhanced CT
Non-resectable
Resectable
Supportive treatment
Consider palliative chemo/radiotherapy
If gastric outflow obstruction develops
consider bypass
EUS (± biopsy)
Laparoscopy + LUS
Non-resectable
Resectable
Operation

Fig. 1 Protocol for the radiological assessment of patients presenting with obstructive jaundice and a pancreatic mass. CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; LUS, laparoscopic ultrasonography

Image analysis

Tumour was defined as resectable if all the following criteria were met: (1) absence of metastatic disease (liver, peri-

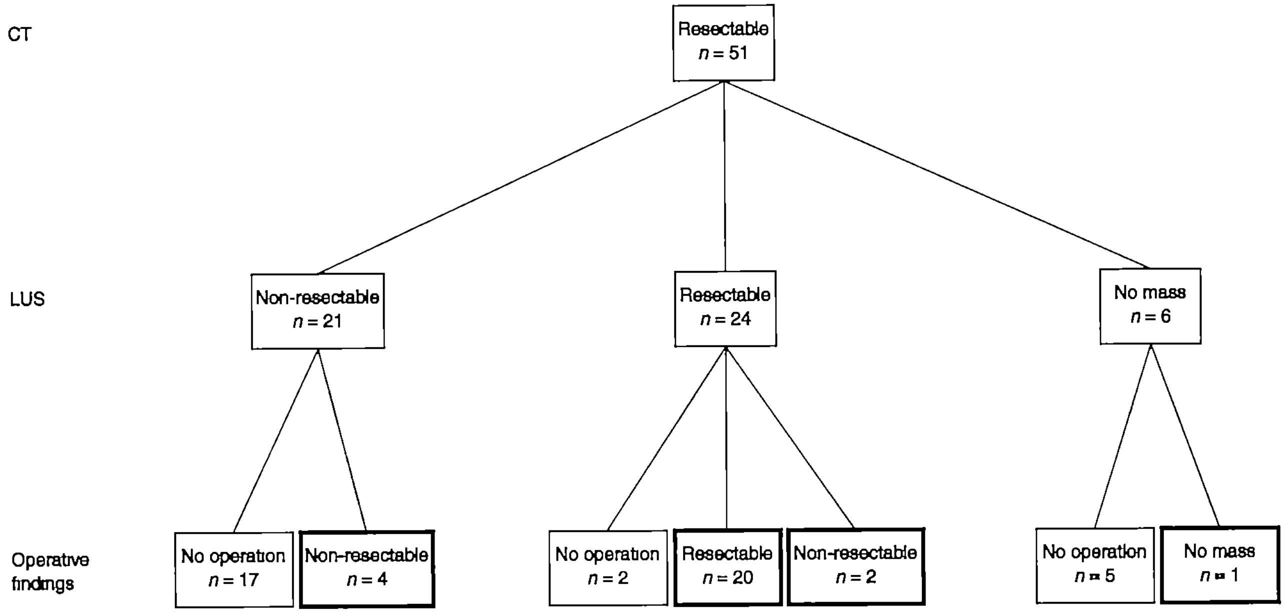


Fig. 2 Results of evaluation by computed tomography (CT) and laparoscopic ultrasonography (LUS), and operative findings in 51 patients with pancreatic tumours

toneum, lymph nodes) and (2) no evidence of local vascular invasion (portal vein, superior mesenteric vein and artery, aorta and inferior vena cava).

All original CT and LUS reports were assessed, and tumours were defined as either resectable or non-resectable according to the above criteria. For all patients who underwent operation, a further retrospective analysis of all images was performed at the end of the study, to establish whether the original reports were considered accurate.

Operative findings

All patients with potentially resectable tumour at LUS were offered a definitive pancreaticoduodenectomy. At operation resectability was defined as complete excision of the tumour, with disease confined to the pancreas or ampulla.

Patients with non-resectable disease were not offered definitive surgery. Non-resectability was supported by biopsy of intra-abdominal metastases (*n* = 8), endoscopic ultrasonography showing vascular invasion (*n* = 9) and laparotomy with biliary bypass (*n* = 4). Selective visceral angiography was not performed to confirm vascular invasion.

Results

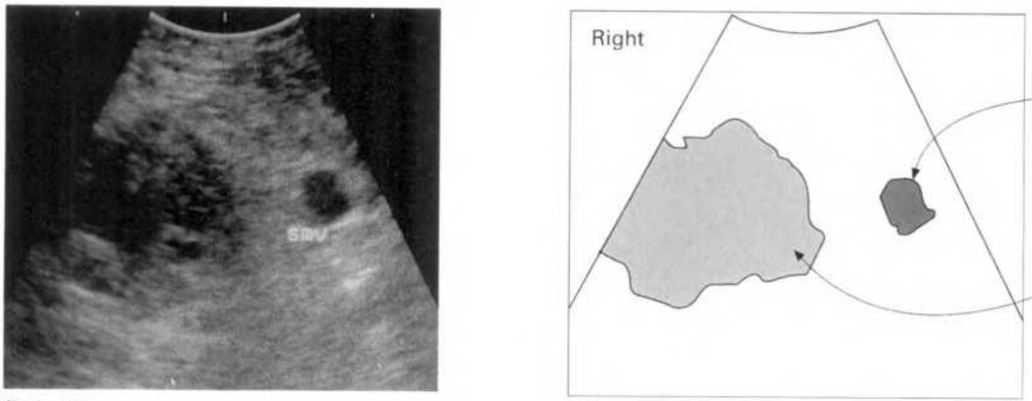
The study contained 51 patients (29 men; mean(s.d.) age 66(10) (range 26–84) years) judged to have resectable disease at CT. Forty-six patients presented with obstructive jaundice and five with pancreatitis. Forty-two patients had lesions in the head of the pancreas and nine patients had ampullary lesions.

Laparoscopic ultrasonography

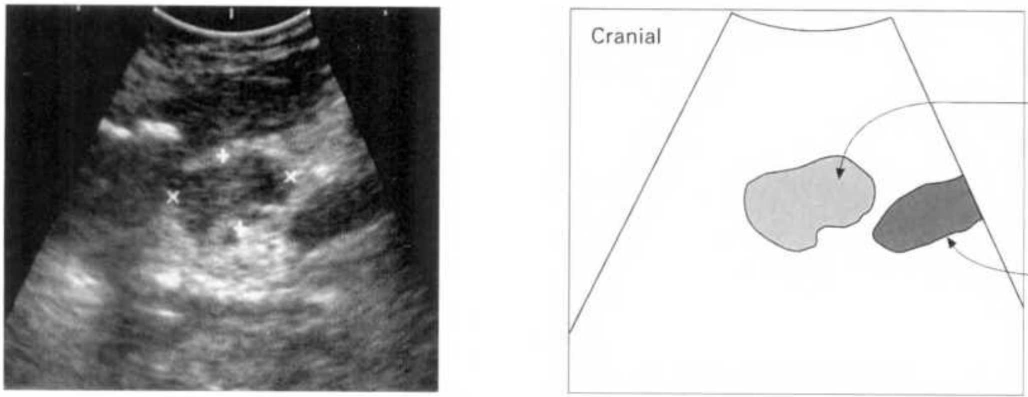
CT and LUS evaluations and operative findings are shown in *Fig. 2*. The mean(s.d.) size of the pancreatic lesions at LUS was 3·0(0·8) (range 1·5–4·5) cm. Twenty-four patients were judged to have resectable disease at LUS (*Fig. 3*). Two of these patients declined surgery, the disease was confirmed as resectable at operation in 20 patients and two patients had non-resectable disease at operation (one with liver metastases and one with vascular invasion). The mean(s.d.) time between LUS and surgery was 17·2(13·7) (range 1–46) days.

Twenty-one patients deemed to have resectable disease at CT were demonstrated to have non-resectable disease at LUS (11 with vascular involvement, seven with liver metastases, four with lymph node involvement, one with malignant ascites and one with peritoneal metastasis); surgery confirmed non-resectability in four patients (laparotomy and biliary bypass). An example of the ability of LUS to demonstrate vascular invasion that was not clearly seen on CT is shown in *Fig. 4*.

Six patients, deemed to have resectable disease at CT, were demonstrated to have non-carcinomatous pancreatic



Patient 1



Patient 2

Fig. 3 Laparoscopic ultrasonographic images (with accompanying line drawings) of resectable head of pancreas tumours from two different patients. For both patients, the tumour is clearly separated from the superior mesenteric vein (SMV) by an area of hyperechoic normal tissue

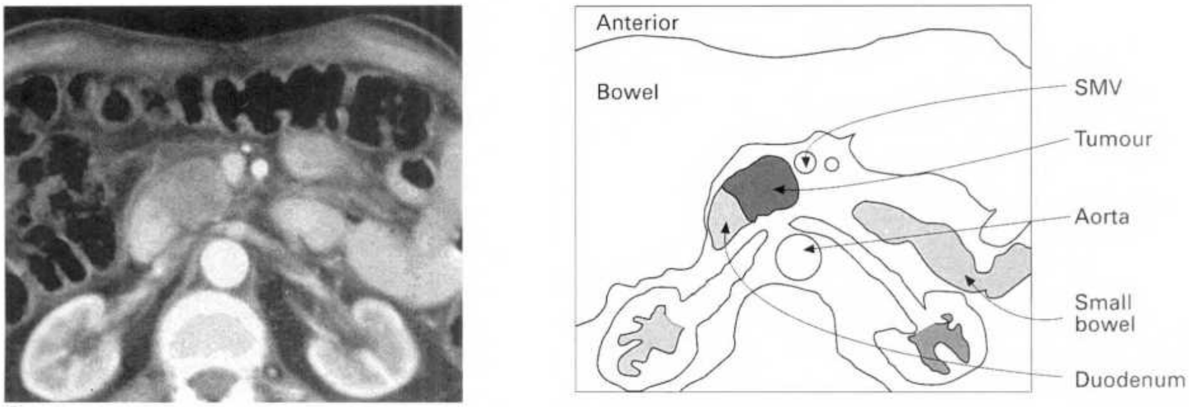
disease at LUS and subsequent investigations. An open cholecystectomy confirmed no pancreatic mass in one patient.

Discussion

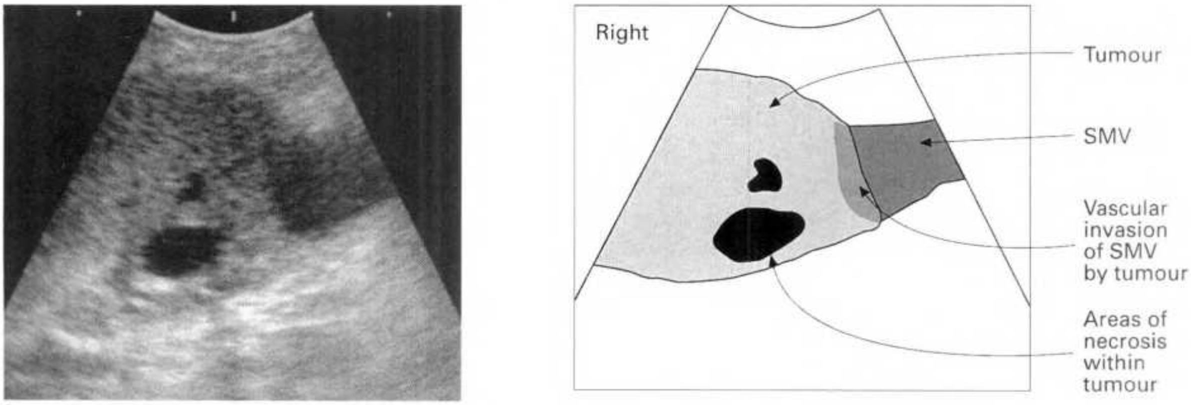
The diagnosis of pancreatic carcinoma carries a poor prognosis[1,2]. However, for patients with resectable disease, 5-year survival rates are improved by radical surgery[3–5], and an accurate assessment of tumour resectability is therefore necessary for optimal patient management. Conventional contrast-enhanced CT has been used for pancreatic tumour staging, but its accuracy for defining resectability can be poor[6]. Additional assessment with laparoscopy has been proposed. In a recent study of 109 patients, laparoscopy identified 29 patients with non-resectable disease that had been defined as 'resectable' at CT[10], confirming the observations of other investigators[8,9]. Further improvement in laparoscopic assessment has been proposed by using direct laparoscopic visualization in combination with LUS. Several studies have demonstrated that LUS can provide staging information additional to that provided by laparoscopy alone, accurately defining tumour resectability (*Table 1*)[11–13].

The aim of the present study was to present an experience with LUS for staging carcinoma of the pancreatic head and periampullary region. LUS was used in all patients who had a CT diagnosis of potentially resectable pancreatic tumour. LUS prevented unnecessary extensive surgery and altered clinical management in 53 per cent of patients (27 of 51). The positive predictive value of LUS was 91 per cent for the 22 patients with LUS-defined resectable disease who underwent surgery.

Tumours in two patients were defined incorrectly as 'resectable' at LUS. For one patient, retrospective analysis revealed misinterpretation of the ultrasonographic images,



a CT


Right
Tumour
SMV
Vascular invasion of SMV by tumour
Areas of necrosis within tumour

b LUS

Fig. 4 Images (with accompanying line drawings) obtained by computed tomography (CT) (**a**) and laparoscopic ultrasonography (LUS) (**b**) from a patient with resectable tumour at CT, which was non-resectable at LUS. The axial computed tomogram (**a**) shows a head of pancreas tumour mass. The adjacent superior mesenteric vein (SMV) does not appear to be involved. On the equivalent axial sonographic image (**b**), from the right flank port, there is tumour invasion of the SMV, with no area of tissue delineation between tumour and vessel. Several areas of tissue necrosis are seen within the tumour

Table 1 Summary of previous studies using laparoscopic ultrasonography, including positive predictive values for defining tumour resectability

		No. of patients with resectable disease			
Reference	Year	CT	LUS	Operative findings	Positive predictive value of LUS (%)
John *et al.*[11]	1995	40	14	11	79
Callery *et al.*[12]	1997	50	28	26	93
Minnard *et al.*[13]	1998	65	39	39	100
Present	2001	51	22	20	91

CT, computed tomography; LUS, laparoscopic ultrasonography

which demonstrated vascular invasion. Importantly, the LUS evaluation of this patient was performed early in the study (third patient enrolled), and by a radiologist who was inexperienced in the technique. This emphasizes the importance of using an experienced imager; at this institution the same surgeon and radiologist now perform all LUS. For the second patient, both endoscopic ultrasonography and LUS suggested potentially resectable disease; however, there was a prolonged delay between radiological evaluation and surgery (46 days). Liver metastases were found at laparotomy in this patient.

For a complete analysis of LUS, ideally a laparotomy should have been performed in all patients, enabling calculation of the true sensitivity and specificity of the technique. Laparotomy was not performed routinely for non-resectable disease defined at LUS, as it would have put this group of patients through an operation that carried no realistic chance of benefit. It is the unfortunate experience of clinicians involved in the management of pancreatic carcinoma that tumours are very rarely less extensive than imaging suggests.

There is some evidence that dual-phase helical CT may provide better staging information than conventional contrast-enhanced CT[18–20]. However, many hospitals still use conventional CT imaging protocols and so the comparison presented in this study remains valid. Magnetic resonance imaging (MRI) has also been used to define pancreatic tumour resectability with positive predictive values of between 77 and 88 per cent[21,22]. However, MRI appears to overestimate vascular invasion; a significant number of patients deemed to have 'non-resectable' disease at MRI undergo definitive resection (5–32 per cent)[21,23] so, at present, MRI alone cannot be used to define non-resectability. More recent preliminary studies indicate that magnetic resonance angiography may improve the detection of vascular invasion[24].

There are numerous modifications to the technique of LUS in the assessment of pancreatic and periampullary tumours. This study used a two-port approach, having been influenced by the Edinburgh group which uses a similar approach and has the largest experience of this technique in the UK[11]. The procedure can be made more complex, for example by opening the lesser sac and performing Kocher's manoeuvre on the duodenum. However, this requires further ports, lengthens the procedure and may increase procedural morbidity and mortality rates. Using the two-port approach, excellent ultrasonographic images of the pancreas were obtained without opening the lesser sac.

From a psychological point of view it is better to perform laparoscopy and LUS as a single short procedure. This is viewed as part of the staging assessment along with endoscopic retrograde cholangiopancreatography and CT. When all the staging procedures have been completed the patient can be prepared properly for a major resection. From an administrative and organizational perspective, it is wasteful to put aside operative time that may not be used if laparoscopy and LUS reveal non-resectable disease.

In conclusion, LUS is an accurate and safe additional investigation for defining tumour resectability and directing management of patients with potentially resectable carcinoma of the pancreatic head or periampullary region. Although LUS is an invasive procedure, requiring a brief general anaesthetic and an overnight stay in hospital, the cost can be offset against the potential expense of an unnecessary laparotomy and a longer hospital stay[25].

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Original article

Liver regeneration after major hepatectomy for biliary cancer

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Background: The aim of this study was to evaluate serial changes in liver volume after major hepatectomy for biliary cancer and to elucidate clinical factors influencing liver regeneration.

Methods: Serial changes in liver volume were determined, using computed tomography, in 81 patients with biliary cancer who underwent right hepatic lobectomy or more extensive liver resection with or without portal vein resection and/or pancreatoduodenectomy. Possible factors influencing liver regeneration were evaluated by univariate and multivariate analyses.

Results: The remnant mean(s.d.) liver volume was 41(8) per cent straight after hepatectomy. This increased rapidly to 59(9) per cent within 2 weeks, then increased more slowly, finally reaching a plateau at 74(12) per cent about 1 year after hepatectomy. The regeneration rate within the first 2 weeks was 16(8) cm^3/day and was not related to the extent of posthepatectomy liver dysfunction. On multivariate analysis, the extent of liver resection ($P < 0.001$), body surface area ($P = 0.02$), combined portal vein resection ($P = 0.024$) and preoperative portal vein embolization ($P = 0.047$) were significantly associated with the liver regeneration rate within the first 2 weeks. In addition, body surface area ($P < 0.001$) and liver function expressed as plasma clearance rate of indocyanine green ($P = 0.01$) were significant determinants of final liver volume 1 year after hepatectomy.

Conclusion: The liver regenerates rapidly in the first 2 weeks after major hepatectomy for biliary cancer. This early regeneration is influenced by four clinical factors. Thereafter, liver regeneration progresses slowly and stops when the liver is three-quarters of its original volume, approximately 6 months to 1 year after hepatectomy.

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Introduction

Normal liver has an enormous regenerative capacity after major hepatectomy[1–3]. After standard 68 per cent hepatectomy in rats, major regeneration occurs during the first 72 h[1,2]. Continued regeneration after 90 per cent hepatectomy in rats implies that a liver regeneration threshold, if it exists, is lower than 10 per cent[3]. Despite extensive research, however, the signals that trigger, regulate and terminate liver regeneration remain unknown[4].

The change in liver volume is an important index of liver regeneration after hepatectomy, which is supported by evidence that total hepatic DNA volume correlates well with liver mass after hepatectomy[5,6]. Although various imaging modalities are available for *in situ* measurement of human liver volume, computed tomography (CT) is the most useful because it is accurate, easy and non-invasive. Many authors have determined liver volume after hepatectomy using CT, finding that human liver has a good regenerative capacity and that regeneration may be influenced by resection volume and the presence of coexisting liver disease[7–16]. Previous studies, however, have involved a limited number of patients, lacked multivariate analysis in all but one study[13], and estimated the rate of regeneration 1 month or later after hepatectomy. In addition, most of the subjects in previous studies were patients with hepatocellular carcinoma or metastatic liver cancer. No study has addressed liver regeneration in patients with biliary cancer, who usually have obstructive jaundice before operation. Hepatectomy for biliary cancer is usually a high-risk procedure[17], often associated with combined pancreatoduodenectomy[18–20] and/or portal vein resection with reconstruction[21,22]. Little is known about the influence of such combined resections on liver regeneration.

In the present study liver volume was measured using CT in patients with biliary cancer who underwent major hepatectomy in order to elucidate clinical factors influencing posthepatectomy liver regeneration.

Patients and methods

From January 1992 to December 1999, 107 patients with biliary cancer underwent right hepatic lobectomy or more extensive liver resection at the First Department of Surgery, Nagoya University Hospital. Of these, three patients were excluded from the study because they died within 1 month. Another 23 patients were excluded because they did not undergo CT at the times mentioned below. Thus, 81 patients were enrolled in this study. All underwent CT at least twice after hepatectomy, first 11–14 (mean(s.d.) 13(1)) days after operation (early stage 1; ES$_1$) and then 26–30 (28(2)) days after operation (ES$_2$). There were 45 men and 36 women, with a mean(s.d.) age of 64(9) years. Forty-nine patients had proximal cholangiocarcinoma and the remaining 32 had advanced gallbladder carcinoma. No patient had cirrhosis. Of the 81 patients, 74 (59 jaundiced and 15 non-jaundiced) underwent preoperative percutaneous transhepatic biliary drainage in order to relieve obstructive jaundice and/or to achieve accurate diagnosis of tumour extent[23,24]. Percutaneous transhepatic portal vein embolization was indicated in 67 patients (83 per cent)[25–27].

Surgical outcome

The surgical procedures performed are summarized in *Table 1*. In patients with jaundice at presentation hepatectomy was done once the serum total bilirubin level had decreased to less than 2 mg/dl following biliary drainage. The tumour was resected curatively in all patients. The mean(s.d.) estimated extent of liver resection was 59(8) (range 43–77) per cent. *En bloc* resection of the caudate lobe and extrahepatic bile duct was performed in all patients. Bilioenteric continuity was re-established with hepaticojejunostomy using a Roux-en-Y jejunal limb. Combined pancreatoduodenectomy was performed in 22 patients (27 per cent) either because of advanced cancer or superficially spreading cancer. Portal vein resection and reconstruction was required in 32 patients (40 per cent). The mean(s.d.) duration of surgery was 787(156) (range 418–1210) min and intraoperative blood loss was 3292(2199) (range 900–14 743) ml. All patients received parenteral nutritional support for at least 7–10 days after hepatectomy. Of the 81 patients, 26 (32 per cent) developed posthepatectomy liver failure, defined as an increased serum total bilirubin concentration above 10 mg/dl. Eighteen of these patients recovered and were well when they left hospital and eight died from liver failure or recurrent disease between 2 and 5 months after operation. The remaining 55 patients made a good postoperative recovery.

Table 1 Surgical procedures performed in 81 patients with biliary tract carcinoma

Type of hepatectomy*	Total	With PD	With PV
S1, 4, 5, 6, 7, 8	15	3	7
S1, 4a, 5, 6, 7, 8	28	12	15
S1, 5, 6, 7, 8	30	7	9
S1, 2, 3, 4, 5, 8	8	0	1

*Expressed as Couinaud's hepatic segments resected. 4a, Inferior part of segment 4. PD, pancreatoduodenectomy; PV, portal vein resection and reconstruction

Liver regeneration

Serial CT scans were analysed after operation to measure liver regeneration. Of the 81 patients, 41 underwent follow-up CT 6–8 (mean(s.d.) 7(1)) months after surgery (late stage 1; LS$_1$) and 12–14 (13(1)) months after surgery (LS$_2$). In addition, 26 of the 41 patients underwent CT over 18 months after surgery (25(4) months; LS$_3$). At each follow-up CT scan, the patients were in good condition without any clinical sign of recurrence.

Volumetric measurement of the liver was performed according to methods reported previously[9,28]. Briefly, serial transverse scans were obtained at 1 cm intervals from the dome of the liver to the most inferior part of the organ, with enhancement by intravenous bolus injection of contrast medium. Each slice of the liver was traced with the cursor and the corresponding area was calculated by computer. The total volume of the liver was obtained by adding the volumes of the individual slices. All volumetric measurements were carried out by a single doctor to minimize interobserver variability.

Liver function variables, including serum total bilirubin, albumin and aspartate aminotransferase (AST) concentrations, were measured regularly before and after surgery, using standard laboratory methods. An indocyanine green test was carried out within 1 week before surgery according to a method described elsewhere[29], and expressed as the plasma clearance rate (KICG). An oral glucose tolerance test was also performed within the week before surgery, and the pattern was classified as parabolic or linear[17]. Body surface area was calculated using the equation of Du Bois[30]: body surface area (m^2) = body-weight (kg)$^{0\cdot425}$ × body height (cm)$^{0\cdot725}$ × 0·007184.

Results are expressed as mean(s.d.). Statistical analysis was performed with paired or unpaired Student's *t* test, where appropriate. All *r* values were defined using Pearson's correlation coefficient. Multivariate analysis was performed with analysis of covariance (ANCOVA) that was programmed into the SAS version 6.12 software (SAS Institute, Cary, North Carolina, USA). $P < 0{\cdot}05$ was considered statistically significant.

Results

Serial changes in remnant liver volume after hepatectomy

The estimated remnant liver volume, expressed as a percentage of the preoperative size, was 41(8) per cent at the time of hepatectomy (*Fig. 1*). The liver volume rapidly increased to 59(9) per cent at the time of ES_1, then slowly increased to 63(11) per cent at the time of ES_2. Thereafter, there was a gradual increase; the liver volume reached 71(13) per cent at the time of LS_1 and 74(12) per cent at the time of LS_2. The difference in liver volume between LS_1 and LS_2 was small but statistically significant ($P < 0{\cdot}001$). However, the liver volume at the time of LS_3 was not statistically different from that at LS_2, indicating that liver regeneration reached a plateau approximately 6 months to 1 year after hepatectomy. The liver regained over 90 per cent of its preoperative size in only five of the 41 patients whose liver volume was measured at the time of LS_2. Serial changes in mean remnant liver volume until LS_2 were well extrapolated with the formula: remnant liver volume (%) = 42·2 + 5·65 × log(days after hepatectomy) (*Fig. 2*).

Early liver regeneration

The liver regeneration rate within 1 month after surgery was evaluated at the two different time intervals: regeneration rate I = (liver volume at ES_1 (11–14 days after surgery) – estimated remnant liver volume at surgery)/days between surgery and ES_1; and regeneration rate II = (liver volume at ES_2 (26–30 days after surgery) – liver volume at ES_1)/days between ES_1 and ES_2. Regeneration rates I and II were 16(8) (range 1–31) and 2(5) (range – 10 to 13) cm^3/day respectively ($P < 0{\cdot}001$). Of the 81 patients, only two (2 per cent) had a larger regeneration rate II compared with rate I. A negative regeneration rate I was not found, whereas a negative regeneration rate II was observed in 21 patients (26 per cent). No correlation was found between regeneration rates I and II ($r = 0{\cdot}033$, $P = 0{\cdot}768$).

Regeneration rate I was not associated with postoperative serum total bilirubin level, which reflects the extent of posthepatectomy liver dysfunction. There was no significant difference in regeneration rate I when 55 patients without liver failure were compared with 26 patents who had liver failure (16(7) *versus* 18(9) cm^3/day). Similarly, there was no significant difference in regeneration rate I between 73 survivors and eight patients who died (16(8) *versus* 17(7) cm^3/day).

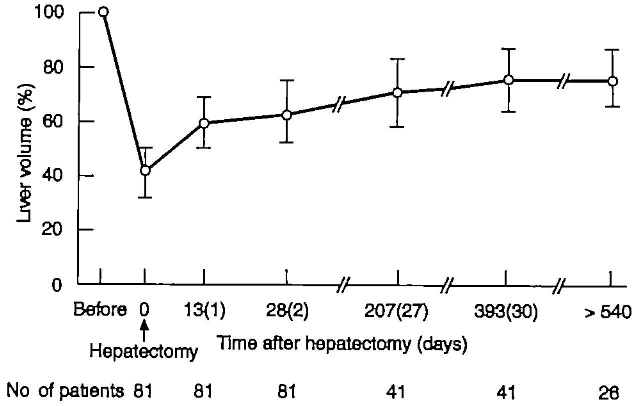
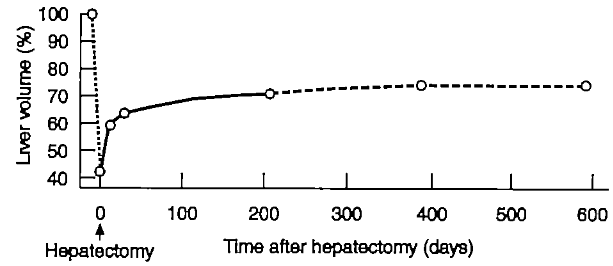
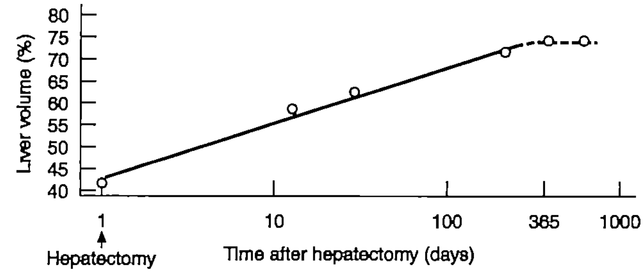


Fig. 1 Serial changes in percentage liver volume after hepatectomy. Values are expressed as mean(s.d.)



a Linear plot



b Logarithmic plot

Fig. 2 Serial changes in mean percentage liver volume after hepatectomy. Data points represent means plotted against time, represented linearly (a) or logarithmically (b). Changes in remnant liver volume within 1 year after hepatectomy (solid line) were extrapolated with the formula: remnant liver volume (%) = 42·2 + 5·65 × log(days after hepatectomy)

Analysis of clinical factors influencing early regeneration

Most of the early regeneration process was completed within the first 2 weeks after hepatectomy. Therefore, 12 independent preoperative and perioperative variables were analysed univariately as possible factors influencing early regeneration. AST concentration on day 1 was a postoperative variable, but was included for analysis because it has been reported to reflect liver injury during surgery[31]. On univariate analysis, regeneration rate I was not significantly related to five dichotomous variables including sex, preoperative glucose tolerance pattern, preoperative portal vein embolization, combined pancreatoduodenectomy and combined portal vein resection (*Table 2*). Regeneration rate I significantly correlated with age ($r = -0\cdot314$, $P = 0\cdot004$), body surface area ($r = 0\cdot222$, $P = 0\cdot046$) and extent of liver resection ($r = 0\cdot456$, $P < 0\cdot001$) (*Table 3*).

Table 2 Univariate analysis of dichotomous clinical variables influencing regeneration rate I (11–14 days after operation)

	No. of patients	Regeneration rate I (cm^3/day)	P*
All patients	81	16(8)	–
Sex			
Men	45	17(8)	0·183
Women	36	15(7)	
Preoperative glucose tolerance			
Linear pattern	14	16(9)	0·82
Parabolic pattern	67	16(8)	
Preoperative portal vein embolization			
Yes	67	16(8)	0·145
No	14	19(9)	
Combined pancreatoduodenectomy			
Yes	22	16(7)	0·919
No	59	16(8)	
Combined portal vein resection			
Yes	32	15(8)	0·417
No	49	17(8)	

Values are mean(s.d.). *Student's t test

Multivariate analysis was done including the three significant factors determined by univariate analysis and six other factors: KICG, total bilirubin on admission, sex, preoperative portal vein embolization, combined pancreatoduodenectomy and combined portal vein resection. These six factors were involved because they were thought to be important clinically. Multivariate analysis demonstrated that extent of liver resection ($P < 0\cdot001$), body surface area ($P = 0\cdot02$), combined portal vein resection ($P = 0\cdot024$) and preoperative portal vein embolization ($P = 0\cdot047$) were significantly associated with regeneration rate I (*Table 4*). The fact that combined portal vein resection and preoperative portal vein embolization became significant on multivariate analysis is explained by the distribution of these factors in the patient group. Twenty-two (33 per cent) of the 67 patients with portal vein embolization underwent portal vein resection, while ten of the 14 patients who did not have portal vein embolization underwent portal vein resection ($P = 0\cdot007$, χ^2 test). Because of this 'ill balanced' distribution, the effects of the two factors offset each other and may have been underestimated on univariate analysis.

Analysis of clinical factors influencing final liver volume

Liver regeneration reached a plateau approximately 1 year after hepatectomy, so the liver volume at the time of LS$_2$ (12–14 months after surgery) was considered to be the 'regenerated' liver volume. Eleven independent clinical

Table 3 Univariate analysis of continuous clinical variables influencing regeneration rate I

	Mean(s.d.) (range)	Correlation coefficient	P
Preoperative			
Age (years)	64(9) (37–80)	– 0·314	0·004
Body surface area (m^2)	1·51(0·16) (1·11–1·96)	0·222	0·046
Total bilirubin on admission (mg/dl)	7·5(6·7) (0·3–30·8)	0·167	0·136
KICG (within 7 days of surgery)	0·157(0·034) (0·073–0·224)	0·130	0·248
Perioperative			
Extent of liver resection (%)	59(8) (43–77)	0·456	< 0·001
Intraoperative blood loss (ml)	3292(2199) (900–14 743)	0·030	0·793
Postoperative			
Serum AST on day 1 (units/l)	453(493) (62–2700)	– 0·057	0·616

KICG, plasma clearance rate of indocyanine green; AST, aspartate aminotransferase

Table 4 Results of multivariate analysis for clinical variables influencing liver regeneration

	Multivariate analysis (ANCOVA)		
	Estimate	s.e. of estimate	*P*
Regeneration rate I (cm^3/day)			
Extent of liver resection	0·5	0·1	< 0·001
Body surface area	16·0	6·7	0·02
Combined portal vein resection	− 3·7	1·6	0·024
Preoperative portal vein embolization	− 4·2	2·1	0·047
Liver volume 1 year after hepatectomy (cm^3)			
Body surface area	612·7	138·3	< 0·001
KICG	1316·5	478·4	0·01

KICG, plasma clearance rate of indocyanine green. ANCOVA, analysis of covariance

variables were analysed as possible determinants of the regenerated liver volume (*Tables 5 and 6*). On univariate analysis, body surface area was highly correlated with regenerated liver volume ($r = 0·829$, $P < 0·0001$) (*Fig. 3*). Although sex was also identified as a significant factor, this apparently resulted from the difference in body surface area between men and women. Clinical factors, including preoperative obstructive jaundice, combined pancreatoduodenectomy and posthepatectomy liver failure, were not related to regenerated liver volume.

Multivariate analysis was performed using the same nine factors included in the multivariate model for regeneration rate I. On multivariate analysis, body surface area ($P < 0·001$) and KICG ($P = 0·01$) were shown to be significant determinants of the regenerated liver volume (*Table 4*). In this analysis, body surface area explained about 70 per cent of the variance in regenerated liver volume. In contrast, KICG explained only 5 per cent of the variance. This indicated that KICG had a relatively small effect after adjustment for the strong influence of body surface area using ANCOVA.

Discussion

In this series, the mean remnant was 41 per cent of the original volume at the time of surgery, increased to 59 per cent on day 12–14, and reached a plateau at 74 per cent about 1 year later. The remnant liver volume increased logarithmically with time after hepatectomy. Nearly two-thirds of the regeneration process appears to be completed within only 2 weeks of major hepatectomy. This rapid volume restoration, however, may be overestimated owing to postoperative vascular engorgement or oedema. In fact, the liver volume at ES_2 was less than that at ES_1 in 26 per cent of the patients. Yamanaka *et al.*[9] reported that the regeneration process in normal human liver after massive resection consists of an early rapid increase, a subsequent decrease then a late slow increase. They suspected that the second phase, a decline in liver volume, is partially due to reduction in liver oedema. Regardless, it is clear that human liver regenerates rapidly within the first 2 weeks after major hepatectomy and slowly thereafter.

Table 5 Univariate analysis of dichotomous clinical variables influencing liver volume 1 year after hepatectomy

	No. of patients	Liver volume (cm^3)	*P**
All patients	41	812(149)	–
Sex			
Men	25	895(108)	< 0·001
Women	16	682(108)	
Preoperative obstructive jaundice			
Yes	25	797(146)	0·449
No	16	834(157)	
Preoperative glucose tolerance			
Linear pattern	5	918(105)	0·09
Parabolic pattern	36	797(150)	
Preoperative portal vein embolization			
Yes	29	804(164)	0·634
No	12	829(111)	
Combined pancreatoduodenectomy			
Yes	7	721(110)	0·089
No	34	830(151)	
Combined portal vein resection			
Yes	12	783(99)	0·435
No	29	824(166)	
Posthepatectomy liver failure			
Yes	11	846(131)	0·375
No	30	799(156)	

Values are mean(s.d.). *Student's *t* test

The mean regeneration rate within 1 month after 50 per cent or more extensive hepatectomy for metastatic liver cancer or hepatocellular carcinoma has been reported to be 20 cm^3/day in normal liver, 11 cm^3/day in chronic hepatitis and 8 cm^3/day in cirrhosis[9]. Considering early rapid regeneration, the rate within the first 2 weeks may be as high as 30 cm^3/day in normal liver and 20 cm^3/day in chronic hepatitis or cirrhosis[9]. Compared with these observations, the early regeneration rate of 16 cm^3/day in the present study was low. Possible reasons for this low rate are that most of the patients had an injured liver owing to obstructive jaundice, the magnitude of the surgery was much greater and preoperative portal vein embolization was used in many patients. Another possibility is that most patients had biliary drainage externally through a percutaneous catheter before surgery, or for 2–3 weeks after

Table 6 Univariate analysis of continuous clinical variables influencing liver volume 1 year after hepatectomy

	Mean(s.d.) (range)	Correlation coefficient	P
Age (years)	62(9) (37–78)	− 0·258	0·103
Body surface area (m^2)	1·52(0·15) (1·26–1·96)	0·829	< 0·001
KICG (within 7 days of surgery)	0·157(0·031) (0·095–0·224)	0·264	0·095
Extent of liver resection (%)	59(8) (45–77)	0·142	0·379

KICG, plasma clearance rate of indocyanine green

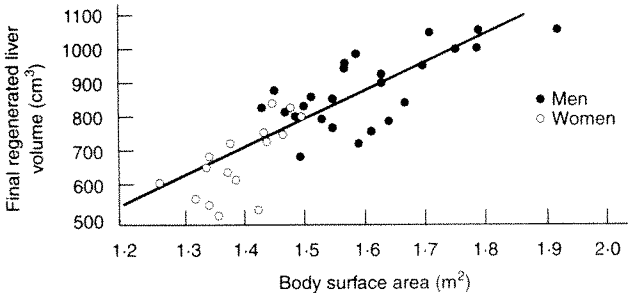


Fig. 3 Correlation between liver volume 12–14 months after surgery and body surface area ($r = 0{\cdot}829$, $P < 0{\cdot}001$)

operation through a transjejunal or transhepatic tube placed at surgery. Suzuki *et al.*[32] and Saiki *et al.*[33] have reported that liver regeneration and function after hepatectomy are better in rats with obstructive jaundice treated by internal drainage than in those treated by external drainage. It has been shown previously that the active form of hepatocyte growth factor is richly excreted into bile after hepatectomy, in proportion to the extent of liver resection[34–36]. Disruption of the enterohepatic circulation of bile-containing growth factors by external biliary drainage may impair liver regeneration.

Human liver regeneration after hepatectomy is influenced by several clinical factors, including the extent of liver resection[7–9,11–13], liver function[9–13,15,16], age[10] and hepatotrophic factors in the portal blood[37,38]. The general conclusion from experimental studies[2,39,40] is that the regeneration rate after hepatectomy is proportional to the extent of resection, whether or not coexisting liver disease is present. This may be related to an increase in portal blood flow containing hepatotrophic factors per unit weight of remnant liver tissue in patients undergoing larger resections. The present study also confirmed that the extent of liver resection is the most significant factor influencing early regeneration. It is logical that body surface area and preoperative portal vein embolization were significant factors influencing early regeneration. When the same percentage of the liver is resected, the absolute volume of resected liver varies according to the patient's body size, represented by body surface area. Regeneration rate would therefore be expected to be associated with body surface area, since liver regeneration is thought to be a process of restoration of the liver to a volume suitable for body size[41]. Portal vein embolization induces regeneration of the future remnant liver before operation[25–27]. Therefore, liver regeneration is likely to be reduced after hepatectomy that follows portal vein embolization. Thanks to this preoperative regeneration, the energy demand required for postoperative regeneration can be reduced, which makes hepatectomy safer.

The multivariate analysis showed that combined portal vein resection was also a factor that significantly influenced early regeneration. The duration of portal vein clamping during portal vein resection was only 20(8) min in this series, and all portal vein resections were performed without intraoperative or postoperative complications. The patency of the reconstructed portal vein was verified in all patients. Thus, the reasons for this association remain unclear. In contrast, it was counterintuitive that combined pancreatoduodenectomy was not selected as a significant factor, because the latter appears to be more invasive than combined portal vein resection. In addition, secretion of insulin, one of the hepatotrophic factors present in portal blood[17,38], is likely to decrease after pancreatoduodenectomy. Rikiyama *et al.*[42] studied rats with 70 per cent hepatectomy alone, or in combination with 70 per cent pancreatectomy; the remnant liver weight and DNA synthesis of hepatocytes were significantly lower in rats after hepatectomy with pancreatectomy. Further study of this issue will be necessary.

Several studies have reported a relationship between liver regeneration and preoperative liver function[9–13,15,16], whereas none has yet described an association between liver regeneration and postoperative liver function. The present study revealed that early liver regeneration had no relation to the extent of postoperative liver dysfunction expressed as serum total bilirubin concentration. No significant difference was observed in early regeneration between patients with or without liver failure. This observation may be explained by the fact that most cases of liver failure after hepatectomy for biliary cancer were related to septic complications which usually develop over 5–7 days after surgery[43]. Regardless, it is important to note that morphological regeneration does not necessarily reflect liver function.

The present study has demonstrated that liver regeneration terminates when the liver has regained about three-quarters of its original size about 1 year after hepatectomy. The liver regained over 90 per cent of its preoperative size in only five of the 41 patients whose liver volume was measured over 1 year after hepatectomy. These findings are compatible with a recent report by Miyagawa *et al.*[14]. Regenerated liver volume was influenced more by body surface area and KICG, than by age, extent of liver resection, the presence of preoperative obstructive jaundice, posthepatectomy liver failure, or combined organ resection. In both clinical and experimental studies on liver transplantation[41,44], the major determinant of final graft size after transplantation is recipient body size. The strong correlation between body surface area and regenerated liver volume observed in the present study suggests that body surface area is a major determinant of eventual liver volume after major hepatectomy, as it is after transplantation. Since KICG is influenced by hepatic blood flow and intrinsic hepatic function, these two factors may also relate to regenerated liver volume[14]. Neither combined portal vein resection nor pancreatoduodenectomy influenced regenerated liver volume.

In conclusion, the liver regenerates rapidly within the first 2 weeks after major hepatectomy for biliary cancer. This early rapid regeneration is determined by the extent of liver resection, body surface area, combined portal vein resection and preoperative portal vein embolization, but is not influenced by the extent of postoperative liver dysfunction. Thereafter, liver regeneration progresses slowly and terminates when the liver has regained three-quarters of its original volume, approximately 6 months to 1 year after hepatectomy. The final volume of regenerated liver may be predicted by body surface area and KICG.

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Original article

Gender differences in long-term survival of patients with colorectal cancer

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Background: Significant differences exist in the immunological response to surgery. This raises the possibility that gender differences exist concerning the outcome after curative colorectal cancer resection.

Methods: To study this hypothesis, a database of patients with colorectal cancer was analysed prospectively.

Results: Some 894 patients were included, 500 (55·9 per cent) were men and 394 (44·1 per cent) were women. Median follow-up was 54·5 months for the entire group and 63·3 months for survivors. The mean(s.e.m.) patient age was 65·3(0·4) years (women 66·1(0·6), men 64·7(0·5) years; $P < 0.05$). Women lived significantly longer after cancer resection than men (57·8(1·5) *versus* 52·0(1·3) months; $P < 0.05$, log rank 0·009). Disease-free survival was significantly longer in women than in men (51·6(1·7) *versus* 46·0(1·4) months; $P < 0.05$). Subgroup analysis revealed significant gender differences in Union Internacional Contra la Cancrum (UICC) stages I ($n = 195$, log rank 0·01) and UICC IV ($n = 38$, log rank 0·021). Survival analysis after rectal cancer resection revealed significant advantages for women (log rank 0·02), while no gender differences were detected when comparing patients after resection for colonic cancer. Moreover, patients older than 50 years ($n = 635$) showed significant gender-related survival differences (log rank 0·015).

Conclusion: Significant gender differences following curative rectal cancer resection were observed. In women disease-free and overall survival were significantly longer. Whether or not these gender differences are related to gender-specific immune functions or to other gender-related local or systemic factors remains to be determined.

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Introduction

Colorectal carcinoma is one of the leading causes of cancer death in western Europe and North America[1]. Clinical research has focused on identification of factors that influence postoperative survival after curative cancer resection. The US Centers for Disease Control[2] have reported a gender ratio of 1·7 (M : F) for the 15 leading causes of death, with a 70 per cent higher age-adjusted mortality rate in males than in females. Tissue trauma, surgical stress and general anaesthesia have been reported to induce significant depression of human immune function, influencing individual susceptibility to infectious complications as well as the metastatic rate of tumours[3,4]. Recently, a number of experimental[5–10] and clinical[11–16] studies showed gender differences regarding post-traumatic immune functions, with significant advantages for women. These gender differences could be explained by the immunological effects of sex steroids, as testosterone has detrimental effects on immunity whereas female sex steroids exert immune-stimulatory effects[7–10].

The reported post-traumatic immune differences, as well as the mentioned effects of immune dysfunction, led to the hypothesis that disease-free and overall survival after curative colorectal cancer resection might be better in women than in men. To study this hypothesis a large single-institution prospective follow-up database was analysed to determine whether or not gender differences regarding disease-free and overall survival could be detected. Survival differences between men and women after colorectal cancer resection may ultimately lead to the detection of novel therapeutic options for patients with colorectal cancer.

Patients and methods

Between January 1990 and December 1995, 894 patients underwent curative resection of large bowel cancer in the department of surgery of Ludwig-Maximilians University. Patient information and follow-up data were collected prospectively. Preoperative staging included endoscopy and/or barium enema, chest radiography, computed tomography (CT), abdominal ultrasonography and estimation of serum carcinoembryonic antigen (CEA) levels. Follow-up was scheduled every 3 months during the first 2 years after operation and every 6 months thereafter. At 4 years after operation follow-up was annual. Follow-up consisted of physical examination, CEA determination, chest radiography, abdominal ultrasonography, CT, endoscopy and faecal occult blood testing. After curative resection of advanced colorectal cancer pathological tumour (pT) stages (pT_{3-4}, lymph node positive), patients were considered for adjuvant radiochemotherapy (chemotherapy with 5-fluorouracil and radiotherapy with 45 Gy) according to the National Cancer Institute protocol[17].

Disease-free and overall survival were monitored up to August 2000 and analysed regarding possible gender differences. The findings were controlled for the influences of patient age, primary cancer site and surgical procedure as well as tumour stage. Tumours were staged according to the Union Internacional Contra la Cancrum (UICC) classification. Survival analysis considered overall as well as disease-specific survival.

Statistical analysis

Data were analysed using one-way analysis of variance (ANOVA), ANOVA on ranks, Student–Newman–Keuls method, Dunn's test and the χ^2 test, as well as Kaplan–Meier survival analysis. Differences were considered statistically significant at $P < 0.05$. Data are presented as mean(s.e.m.).

Results

Patient demographics

Some 894 patients underwent curative colorectal cancer resection between January 1990 and December 1995 and were available for follow-up to August 2000. The median follow-up of the entire study group was 54·5 months, and follow-up of survivors was 63·3 months. Mean(s.e.m.) patient age was 65·3(0·4) years and men (*n* = 500, 55·9 per cent) were significantly younger (mean(s.e.m.) 64·7(0·5) years) than women (*n* = 394, 44·1 per cent; 66·1(0·6) years; $P < 0.05$) at the time of primary cancer resection. Tumour stages were equally distributed among men and women (*Fig. 1*). Most patients presented with UICC IIa colorectal cancer (*n* = 294, 32·9 per cent). A mean(s.e.m.) of 17·3(0·3) lymph nodes were removed with the cancer-bearing specimen and no gender differences regarding the number of lymph nodes removed during operation were detected (men 17·5(0·4) *versus* women 16·9(0·6)). Disease-specific survival data are available for 729 patients (400 men, 329 women). Among these patients, women were significantly older than men (64·5(0·7) *versus* 62·9(0·5) years; $P < 0.05$).

Surgical procedures

More than half of both patient groups underwent curative resection of rectal cancer (men 57·0 per cent *versus* women 53·8 per cent) and the most frequent surgical procedure performed was anterior rectal resection for both sexes (*Table 1*). Colonic cancer was most frequently treated by right hemicolectomy. No gender differences were observed between men and women regarding primary cancer site or surgical procedures performed for curative cancer resection.

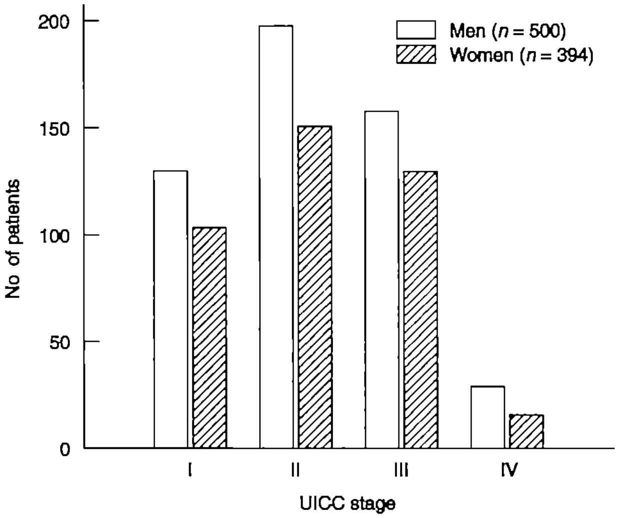
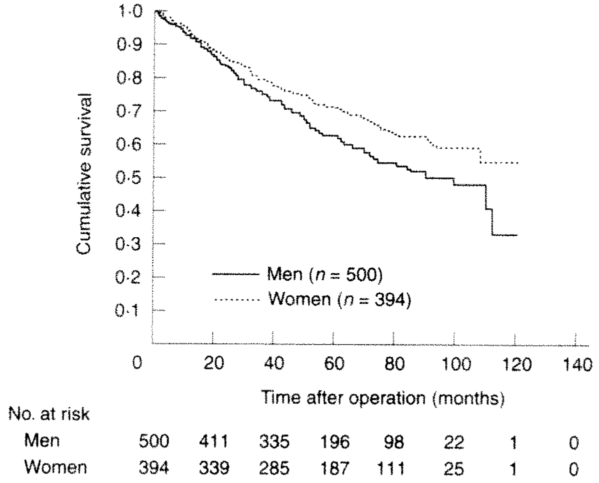


Fig. 1 Tumour stage of patients in the study according to the Union Internacional Contra la Cancrum (UICC) classification

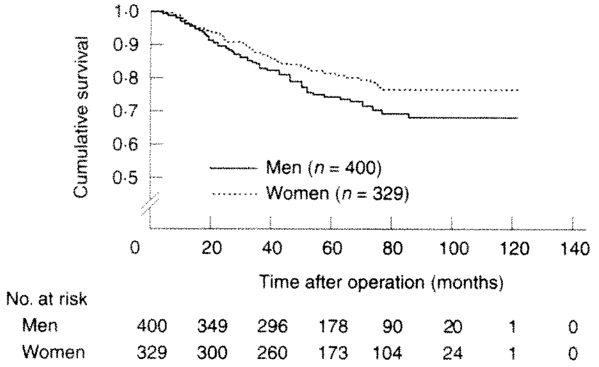
Table 1 Surgical procedures for curative colorectal cancer resection (all ages, all tumour stages)

	Men (n = 500)	Women (n = 394)
Left hemicolectomy	52 (10·4)	36 (9·1)
Right hemicolectomy	96 (19·2)	94 (23·9)
Transverse colonic resection	8 (1·6)	16 (4·1)
Sigmoid resection	56 (11·2)	35 (8·9)
Total colectomy	3 (0·6)	1 (0·3)
Abdominoperineal excision	50 (10·0)	36 (9·1)
Anterior rectal resection	226 (45·2)	171 (43·4)
Local resection	9 (1·8)	5 (1·3)

Values in parentheses are percentages



a Overall survival



b Disease-specific survival

Fig. 2 **a** Overall and **b** disease-specific survival analysis in patients of all ages, all Union Internacional Contra la Cancrum tumour stages

Disease-free and overall survival

Within the entire study group significantly longer overall survival (57·8(1·5) *versus* 52·0(1·3) months; $P < 0·05$) (*Fig. 2a*) and disease-free survival (51·6(1·7) *versus* 46·0(1·4) months; $P < 0·05$) were observed among women compared with men. Kaplan–Meier survival analysis confirmed the significantly longer survival of women (log rank 0·009) in the entire study group.

Disease-specific survival

Disease-specific survival data were analysed for 729 patients (400 men, 329 women). Significantly longer periods of disease-free (50·4(1·6) *versus* 56·2(1·8) months; $P < 0·05$) as well as overall survival (56·5(1·4) *versus* 62·3(1·6) months; $P < 0·05$, log rank 0·041) (*Fig. 2b*) were observed in women, who were significantly older than men (62·9(0·5) *versus* 64·5(0·7) years; $P < 0·05$).

Influence of tumour stage on disease-specific survival

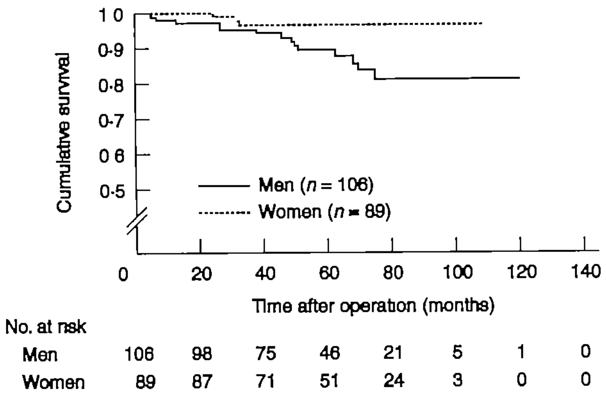
Comparison of tumour stage-related survival of male and female patients revealed significantly better survival of lymph node-negative pT_1 and pT_2 (UICC I) *versus* lymph node-negative pT_3 and pT_4 (UICC II) colorectal cancer (log rank < 0·001, data not shown). Furthermore, patients with lymph node positive disease (UICC III) or distant metastases (UICC IV) showed significantly poorer long-term survival than those with less advanced cancer stages (log rank < 0·001, data not shown).

Among patients suffering from UICC I colorectal cancer, disease-specific survival was significantly longer in women than in men after curative cancer resection (71·9(2·4) *versus* 64·9(2·5) months; $P < 0·05$, log rank 0·01) (*Fig. 3a*). No gender differences were observed regarding patient age or disease-free survival. No gender differences were detected in patients with UICC II or UICC III colorectal cancer with respect to patient age, disease-free or overall survival.

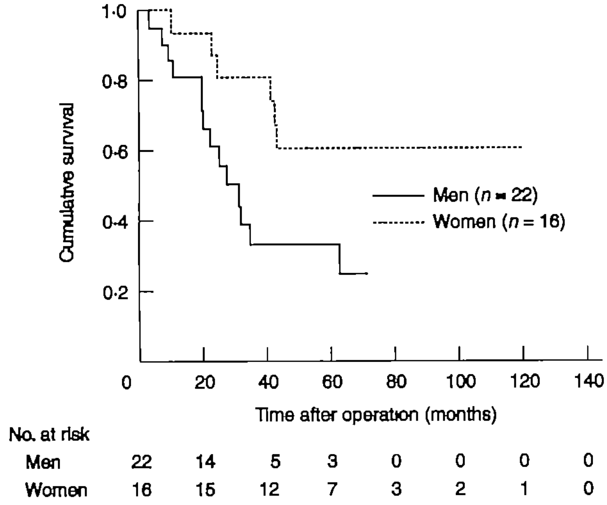
Women with advanced colorectal cancer of UICC IV were of equal age to corresponding male patients. Kaplan–Meier analysis showed significant postoperative disease-specific (30·1(4·4) *versus* 59·4(8·0) months; $P < 0·05$, log rank 0·021) and disease-free (14·4(4·6) *versus* 42·0(10·5) months; $P < 0·05$) survival advantages among the women in this group (*Fig. 3b*).

Influence of patient age on disease-specific survival

Among patients younger than 50 years of age (29 per cent of all patients) no gender differences were detected regard-



a Stage I



b Stage IV

Fig. 3 a Disease-specific survival analysis in patients of all ages: a Union Internacional Contra la Cancrum (UICC) stage I; b UICC stage IV

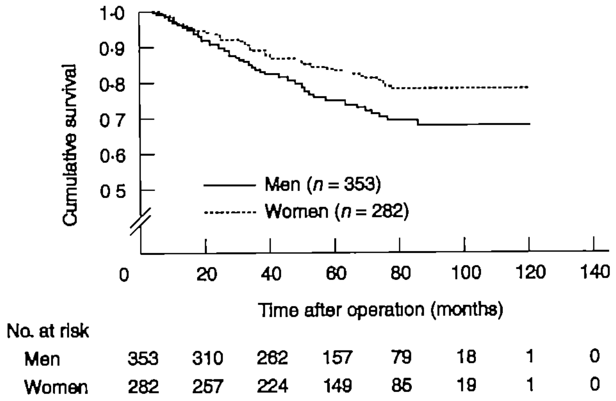


Fig. 4 Disease-specific survival analysis in patients aged over 50 years, all Union Internacional Contra la Cancrum tumour stages

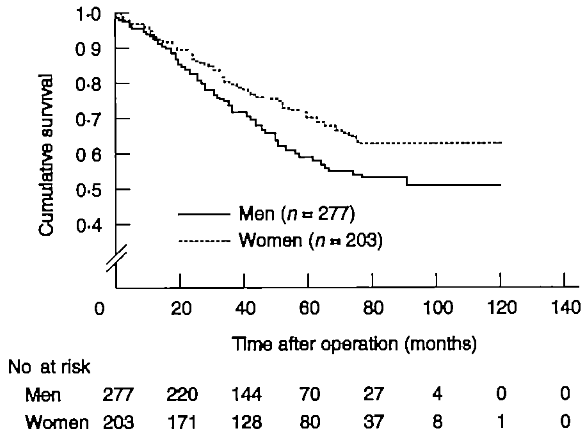


Fig. 5 Disease-specific survival analysis in patients with cancer of the rectum, all Union Internacional Contra la Cancrum tumour stages

ing disease-free or overall survival after curative colorectal cancer resection. Among patients over 50 years of age (71 per cent of the entire study group) women were significantly older than men (62·3(1·6) *versus* 56·5(1·4) years; $P < 0.05$). Significant gender differences regarding disease-free (men 50·4(1·4) months *versus* women 56·2(1·8) months; $P < 0.05$) and disease-specific (56·5(1·4) *versus* 62·3(1·6) months; $P < 0.05$) survival were observed (*Fig. 4*). Kaplan–Meier survival analysis confirmed these significant gender differences (log rank 0·015).

Influence of primary cancer site on disease-specific survival

Some 65·8 per cent ($n = 480$) of all patients had rectal cancer. Significant gender differences were detected regarding disease-free (men 41·8(1·9) months *versus* women 50·5(2·5) months; $P < 0.05$) and disease-specific (49·3(1·6) *versus* 57·9(2·1) months; $P < 0.05$) survival (*Fig. 5*). Kaplan–Meier survival analysis confirmed these significant gender differences in patients suffering from rectal cancer (log rank 0·02). There were no significant gender differences regarding patient age, disease-free or overall survival among patients with colonic cancer.

Discussion

In western Europe colorectal carcinoma develops with an incidence of approximately 0·7 per cent per year, newly affecting 450 per 100 000 population with colonic cancer and 240 per 100 000 population with rectal cancer. More than two-thirds of these patients undergo curative primary tumour resection; none the less more than half of the patients eventually die from the disease following surgery[18,19]. During recent years outcome research has therefore focused on the identification of factors that influence postoperative survival after curative cancer resection.

As far as gender differences in patients with colorectal cancer are concerned, in women no clear associations between socioeconomic status indicators and colonic cancer were observed, whereas in men a significant association between social standing and cancer risk has been detected[20]. Furthermore, significant gender differences regarding the predominant sites of colorectal cancer have been reported, with women tending to have a higher incidence of cancer of the right colon while males mostly develop cancer of the left colon and rectum[21]. The reported gender differences are of special interest as genetic factors or differences in the distribution of risk factors may be involved and be of prognostic relevance.

Significant survival differences between men and women have been reported by the US Centers for Disease Control[2] which were subsequently confirmed by a number of experimental[5–10,22] and clinical[11–16] studies. The present authors therefore hypothesized that survival after curative colorectal cancer resection might be better in women than in men. To study this hypothesis a large single-institution prospective follow-up database was analysed to determine whether or not gender differences regarding disease-free and overall survival could be detected after surgery for colorectal cancer. It has been shown that 80 per cent of all recurrences develop within the first 2 years of curative resection of colorectal cancer[23,24]. A medium follow-up interval of 55 months was chosen to ensure detection of most cancer relapses during the study period.

The proposed immunological factors that influence outcome following resection of colorectal cancer are of importance because recent clinical studies have demonstrated the prognostic relevance of circulating immune parameters for the outcome of patients undergoing such resection[25,26]. Belluco *et al.*[25] reported that an interleukin (IL) 6 concentration of more than 10 pg/ml is an independent negative prognostic marker of survival in patients suffering from colorectal cancer. Shibata and Takekawa[26] demonstrated that serum IL-2 receptor levels can serve as a predictor of progress of colorectal cancer.

The findings of this study clearly indicate significant disease-specific survival advantages for women suffering from rectal cancer, compared with men of equal age and tumour stage. The present study demonstrates significantly longer disease-free and overall survival of women following curative resection of rectal cancer. These gender differences were observed when considering the entire study group. Subgroup analysis revealed that significant differences regarding overall and disease-free survival exist in patients with UICC I as well as UICC IV colorectal cancer. Moreover, in patients older than 50 years and in those with cancer of the rectum, gender differences were detected.

Ten per cent of patients with UICC I colorectal cancer developed recurrent disease, which compares well with the findings of Müller *et al.*[27]. Kaplan–Meier survival analysis revealed significantly better survival of patients with UICC I colorectal cancer when compared with higher tumour stages. Long-term survival of UICC I patients was 86 per cent, which is in agreement with data published by others[28]. The observed gender differences in patients with UICC I cancer appear to be of special interest as the immunological barrier against spread of malignancy is intact in the early stages of colorectal cancer. Better postoperative immunity in women may contribute to better long-term survival in these patients.

The observed gender differences after curative rectal cancer resection are probably due to a number of factors and it is possible that the spread of malignant disease after rectal cancer resection is under the control of immune functions. The significantly better survival of women after resection of rectal cancer therefore supports the hypothesis that better postoperative immune function contributes to superior long-term results in women with colorectal cancer. Gender differences regarding follow-up survival of patients with rectal cancer have also been related to anatomical differences between the male and female pelvis[29]. This notion, however, is not supported by others, who have reported that rectal resection can be radically performed in men just as well as in women[30,31]. The experimental and clinical findings of immunological gender differences must also be considered. Obviously, further studies focusing on the role of immunity for long-term results after colorectal cancer resection are necessary. Additional results may be expected from studies focusing on outcome after laparoscopic rectal cancer surgery, since anatomical sex differences are of less importance and long-term outcome should be comparable in men and women if anatomy is the primary factor influencing follow-up survival. The observed significant gender differences in survival after rectal cancer resection therefore appear to relate to a number of influencing factors. With regard to the influence of general life expectancy on the findings, in 1998 females in Germany had a life expectancy of 80·5 years and males lived for 74·4 years[32]. Female patients were significantly older than males; it can therefore be assumed that differences in gender-dependent life expectancy are not confounding the observations made in this study.

The role of sex steroids in tumour formation and differentiation is unclear. None the less, histopathological studies have revealed specific steroid hormone receptors in the human intestine and in human colonic tumours[33]. Furthermore, messenger RNAs coding for oestrogen and progesterone receptors have been detected in colorectal cancer specimens, although there were no differences between male and female patients[34]. Female sex steroids may therefore exert a protective immunological effect in colorectal cancer, which could explain the better survival of women after curative rectal cancer resection reported here. On the other hand, oestrogen has been reported to have mitogenic effects on colonic cancer cells *in vitro*[35]. Whether or not this is of relevance to the development of colonic cancer in humans remains unclear. Female sex steroids play a minor role in endocrine function in postmenopausal women. It appears, therefore, that the detrimental immunological effects of androgens, as previously observed in a number of animal studies[7,36,37], rather than the protective effects of female sex steroids influence perioperative immune function in patients with colorectal cancer. The current data, however, show no gender differences regarding the incidence and/or survival of colonic cancer. None the less, the lack of significant gender differences among patients with colonic cancer may be explained by the reported mitogenic effects of female sex steroids in colonic cancer cells.

It is not known whether or not gender differences exist regarding the effectiveness of postoperative radiochemotherapy in patients having curative resection of colorectal cancer. In view of the reported differences regarding steroid receptor expression on cancer specimens, this constitutes an interesting aspect for future studies regarding gender-related outcome differences in patients with colorectal cancer[34].

The observed improved outcome after colorectal cancer resection in patients older than 50 years indicates that sex steroids may not be the only factors responsible for better long-term results in women. This interesting observation confirms previous findings regarding gender-related survival of patients with severe sepsis and septic shock in surgical intensive care in that women older than 60 years were found to have a survival advantage[16].

The observed gender differences reported here confirm the findings of a prospective study of 11 000 patients with colorectal cancer that demonstrated a higher survival rate in women than in men[38]. This has also been shown in a study of 50 patients diagnosed with colorectal cancer under the age of 40 years, in which women had significantly better survival than men[39]. Another clinical study, however, did not detect any gender differences in the 5-year survival rate after adjustment for age and extent of disease[40].

In view of the present findings and data in the literature, prospective immunological studies are required to determine whether or not sex steroids or other gender-related factors are of prognostic relevance after curative resection of colorectal cancer. These studies may ultimately contribute to the development of novel therapeutic options for patients suffering from colorectal cancer.

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The Colorectal Cancer Study Group comprises C. Müller, M. W. Wichmann, T. Strauss, R. A. Lang, H. M. Hornung, U. Lau-Werner and G. Kramer.

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Original article

Road traffic fatalities in Victoria, Australia and changes to the trauma care system

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Background: The aim was to identify organizational and clinical errors in the management of road traffic fatalities and to use this information to improve Victoria's trauma care system.

Methods: A multidisciplinary committee evaluated the complete ambulance, hospital and autopsy records of 559 consecutive road traffic fatalities, who were alive on arrival of ambulance services, in five substantial time periods between 1992 and 1998. Patients who survived more than 30 days were excluded. Errors or inadequacies in each phase of management, including those contributing to death, were identified and an assessment was made of the potential preventability of death.

Results: Findings between 1992 and 1998 were similar. In 1998, 1672 problems were identified in 110 deaths with 1024 (61 per cent) contributing to death. Eight hundred and forty-two (50 per cent) of the total problems occurred in the emergency department. There were frequent problems in initial patient reception and medical consultation, resuscitation, investigation and assessment (especially of the abdomen and head), and in transfer to the operating theatre or to a higher-level hospital. Victoria's combined preventable and potentially preventable death rate has been unchanged between 1992 and 1998 (34–38 per cent).

Conclusion: The problems identified led to a Ministerial Taskforce on Trauma and Emergency Services in Victoria as a consequence of which a new trauma system is now being implemented.

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Introduction

By 1992, there was both international recognition that preventable deaths were frequent after severe trauma[1,2] and a lack of information on the quality of trauma care in Australia. In this environment, a Consultative Committee on Road Traffic Fatalities was initiated by the Victorian Road Trauma Committee of the Royal Australasian College of Surgeons and the Victorian Institute of Forensic Medicine (Victoria's statutory forensic pathology provider). Since its establishment the Committee has been funded by the Transport Accident Commission (Victoria's monopoly third-party motor vehicle insurer) and the Department of Human Services. The objectives were to identify organizational and clinical errors or inadequacies in the care of individual road traffic fatalities who were alive on arrival of ambulance services, and to consider whether these problems contributed to the patient's death. In addition the preventability of each death was assessed. These objectives were potentially threatening to the healthcare system. Political will was required to help negotiate a path through the bureaucracy, and to ensure continued funding for the Committee. The Committee's findings have stimulated the development by all stakeholders of a new trauma care system in Victoria, which was introduced in 2000[3].

Approximately 1500 patients per year are admitted with major trauma in Victoria (population 4·6 million), of whom about 70 per cent are road traffic casualties. During this study patients were generally transported by ambulance to the nearest public hospital emergency department. Melbourne's single adult trauma centre also received some patients by helicopter from rural crash scenes and transfers from rural and outer metropolitan hospitals.

Patients and methods

The Consultative Committee consists of two 12-member evaluative committees comprising general surgeons, neurosurgeons, cardiothoracic surgeons, orthopaedic surgeons, emergency physicians, anaesthetists, intensivists, mobile intensive care ambulance (MICA) paramedics (advanced trauma life support (ATLS)-trained) and pathologists. Before fortnightly meetings, each evaluation committee member is forwarded a premeeting analysis prepared and collated by its three member research staff. This includes chronological and clinicopathological analysis of the complete ambulance, hospital and autopsy records, a narrative summary, the deposition to the Coroner, audit filter analysis, and Trauma and Injury Severity Score (TRISS) survival probability of individual fatalities. One committee member is responsible for presentation of the case after reviewing the complete records. Two or three fatalities are discussed at each 90-min meeting during which specific problems are identified and categorized as system inadequacies, errors in treatment or management strategy, errors in technique, delays in diagnosis or errors in diagnosis. After this evaluation has been completed the problems that contributed to death are identified. A problem was assessed as contributing to death if it was considered to favour the probability of death or to shorten survival in an individual patient. The methodology has been detailed previously[4,5].

Although the major focus of the Consultative Committee is the identification of specific problems in trauma care delivery, the Committee additionally makes judgements about preventable deaths. Deaths are classified as non-preventable, potentially preventable or preventable. Preventable is defined as a death in which it is considered in retrospect, with full knowledge of the clinical history and all injuries sustained, that the chance of survival would have been 75 per cent or more had the patient been triaged effectively to a hospital with the appropriate facilities in the minimum of time and appropriate management had been provided promptly. A potentially preventable death is defined as one in which it is considered that the chance of survival was 25–74 per cent, and a non-preventable death one in which the chance of survival was considered less than 25 per cent. Public policy has been influenced by previous peer group preventable death studies and their limitations are recognized[6,7].

Because of previous criticism of preventable death studies[6,7], the Committee assessed the reproducibility of its judgements. Comparison of judgements on the same 60 fatalities assessed independently by each evaluation committee demonstrated high intercommittee and intracommittee Kappa concordance[8]. The Committee's findings since 1992 have been published previously[4,9–12].

Results

Table 1 shows the distribution of problem categories in the different areas of care for 1998, including those contributing to death. Half of all problems occurred in the emergency department, with 60 per cent contributing to death. The more frequent problems encountered in emergency departments are detailed in *Table 2*. Taking all the areas of care together, 87 per cent of all problems contributing to death were management errors, 4 per cent were system inadequacies, 3 per cent technique errors, 2 per cent diagnosis delays and 3 per cent diagnosis errors. Management errors included inadequacies in patient reception and medical consultation, investigation and assessment (e.g. failure to assess the abdomen or head adequately), and delayed transfer to the operating theatre or to a higher-level hospital. During 1998 the combined rate of preventable and potentially preventable deaths was 35 per cent. The overall percentage of preventable and potentially preventable deaths in Victoria has remained virtually unchanged between 1992 and 1998 (*Fig. 1*). TRISS survival

Table 1 Problems identified between 1 January and 31 December 1998 in the emergency and clinical management of 110 fatalities who were alive on arrival of ambulance services

Area of care	Patients	Admissions	No. of problems	No. of problems contributing to death
Prehospital	110	110	254 (15)	177 (70)
Emergency department	99	112	842 (50)	502 (60)
Operating theatre	59	76	226 (14)	143 (63)
Intensive care unit	55	63	221 (13)	129 (58)
Ward/high-dependency unit	13	20	72 (4)	49 (68)
Interhospital transfer	23	28	57 (3)	24 (42)
Total	110	409	1672 (100)	1024 (61)

Values in parentheses are percentages

Table 2 Specific emergency department problems during 1998 in 99 patients

Problem category	No. of problems	No. contributing to death
System inadequacy	14	6
Management error	764	463
Reception and medical consultation	132	72
No consultant general surgeon	34	21
Inadequate documentation	22	0
No or delayed neurosurgical consultation	21	11
Inappropriate medical reception	18	12
No consultant assessment	10	9
Delay in arrival of appropriate consultant	10	7
Inappropriate triage category	10	6
Other	7	6
Resuscitation	238	192
Delayed resuscitation – blood	38	34
Inadequate resuscitation – fluid	37	35
Inadequate resuscitation – blood	26	21
No or delayed chest decompression	21	11
Inadequate resuscitation – respiratory/ventilatory	20	15
Delayed resuscitation – respiratory/ventilatory	18	14
Inadequate resuscitation – clotting factors	17	17
No or delayed second intravenous line	12	5
No stabilized pre/intra CT scan	11	8
Inadequate external haemorrhage control	10	9
Other	28	23
Investigation/assessment	143	58
Inadequate abdominal assessment	39	20
No/inadequate haematology	20	9
Investigation delay	18	9
No or delayed CT head	14	6
Other	52	14
Monitoring	129	63
Infrequent arterial blood gases	59	32
Inadequate perfusion monitoring	28	19
Inadequate observations	28	9
Other	14	3
Other treatment	75	39
Inappropriate drugs/dosage	18	10
Inadequate management of hypothermia	16	12
Other	41	17
Transfer	47	39
Transfer delay – theatre	25	20
Interhospital transfer problems	15	14
Intrahospital transfer problems	7	5
Technique error	12	5
Diagnostic delay	16	15
Abdomen	6	6
Chest	4	3
Other	6	6
Diagnostic error	36	13
Chest	16	3
Head/neck	6	1
Abdomen	5	2
Failure to appreciate severity of injury	5	5
Other	4	2

CT, computed tomography

probability analysis[13] found, with the exception of 1996, little change in the proportion of deaths with survival prospects exceeding 75 per cent (1992–1993, 36 per cent; 1993–1994, 34 per cent; 1996, 20 per cent; 1997, 32 per cent; 1998, 29 per cent). These percentages were much higher than the 4–6 per cent preventable death rates determined by the Committee.

Discussion

Between July 1992 and December 1998, the profile of deficiencies and errors in the trauma care of road traffic fatalities who were alive on arrival of ambulance services, and the preventable death rates have remained essentially unchanged. The combined preventable and potentially preventable death rate was significantly less for Melbourne's single trauma centre (20 per cent) than for the other hospital groups (specialist teaching, 40 per cent; metropolitan non-teaching, 41 per cent; large regional, 53 per cent; small regional, 62 per cent)[14]. The preventable death rates determined by the evaluation committee were less than those indicated using TRISS survival probabilities. This discrepancy is explained, at least in part, by well known deficiencies in TRISS concerning individual patient assessments[5,15–17].

The Consultative Committee's annual reports have been provided to each Victorian hospital receiving major trauma, to the Transport Accident Commission, the Department of Human Services, and to the Ambulance Services, Victoria. Committee members have presented its findings at meetings in all Victorian hospitals receiving major trauma. Despite these attempts to improve the quality of care, with the exception of a reduction in prehospital system inadequacies in rural Victoria consequent upon increasing numbers of ATLS-trained paramedics, no measurable improvement followed. The lack of a central organization responsible for trauma care delivery and management prevented the earlier introduction of system changes to both ambulance services and hospitals. In 1997 the Committee initiated meetings with representatives of the learned colleges and specialist societies to obtain a consensus on the required action[18]. The specific problems identified by the Consultative Committee were used to develop almost 200 recommendations[18]. The Committee's findings and the recommendations were presented to the Minister for Health and led to a Ministerial Taskforce which formulated the implementation of the advised changes[3]. The solution was a statewide integrated trauma care system responsive to the special needs of 'time critical' trauma patients in Victoria[3]. The introduction of an integrated trauma care system has generally (but not universally) been followed by improved results[7,19–21] and a

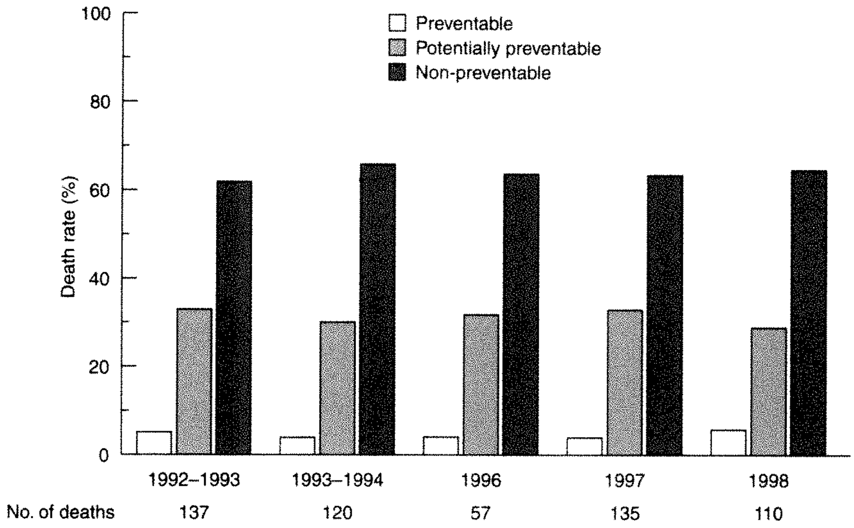

Fig. 1 Preventable, potentially preventable and non-preventable death rates in Victoria 1992–1998 inclusive. The rates remained similar during this interval

'before and after' study is being undertaken by the Committee.

The new integrated trauma care system involves a range of strategies[3].

Trauma system structure

Hospitals are designated to levels within a tiered trauma structure providing different complexities of care and patients with trauma are treated by a service appropriate to the level of care needed. The Major Trauma Services comprise three trauma centres (two adult and one paediatric) in Melbourne which will provide definitive care to the majority of patients with major trauma either transported directly, or referred from other hospitals. A State Trauma Committee will coordinate the system.

Triage

Patients with major trauma identified in the prehospital setting according to specified physiological, anatomical and mechanistic criteria will be triaged to a Major Trauma Service when the patient is less than 30 min away. Otherwise the patient will be triaged to the highest designated trauma service accessible within 30 min or, in isolated rural areas, in the shortest time. After initial stabilization, early liaison with a Major Trauma Service will follow, with consideration given to the need for early medical retrieval and interhospital transfer using helicopter ambulances or fixed-wing aircraft, where appropriate.

Trauma teams

All hospitals designated to receive patients with major trauma will have an immediate formal trauma team response for initial patient reception and management. The trauma team will consist of clinicians from surgical, emergency department and anaesthetic/intensive care unit services. A consultant general surgeon will be present within 15 min of the patient's arrival.

Role of director of trauma services

Trauma services will have a clinician appointed as the director of trauma services with clinical and audit responsibilities.

Communication

Technology and processes will be improved to streamline communication between care providers and the Major Trauma Services will establish a dedicated telephone number for trauma referral and advice.

Retrieval and transfer

Guidelines for interhospital transfer will ensure that patients with trauma are managed in a timely way at the most appropriate hospital.

Audit and quality management

Statewide audit and quality assurance will provide ongoing monitoring of trauma care processes including rehabilitation and quality of life outcomes.

Research, service and technology developments

Recently the Victorian Trauma Foundation has been established with initial funding from the Transport Accident Commission. The Foundation will set priorities for trauma research and educational activities relevant to the trauma system.

Education, injury prevention and training

The provision of education and training programmes will meet the needs of staff from a diversity of disciplines and ensure efficient and effective trauma management. Injury prevention will involve research and community education.

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Original article

Effect of multimodality therapy on circulating vascular endothelial growth factor levels in patients with oesophageal cancer

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Background: Angiogenesis is critical for tumour growth and metastasis. The switch to the angiogenic phenotype depends on the net balance between positive and negative angiogenic factors released by the tumour. It was hypothesized that patients with oesophageal cancer would express raised serum levels of vascular endothelial growth factor (VEGF) which would return to normal values with neoadjuvant chemoradiotherapy.

Methods: Forty-four patients with oesophageal cancer who were selected for treatment with neoadjuvant chemoradiotherapy had blood samples taken before treatment, during chemoradiotherapy, before operation, on days 1, 3 and 5 after surgery, and 3 months after resection. Serum levels of VEGF were measured. Values were correlated with response to treatment. Controls were patients who were undergoing surgery for non-malignant conditions.

Results: Serum VEGF levels were raised in patients with oesophageal cancer compared with age-matched controls (mean 247 *versus* 1157 pg/ml; $P < 0.01$). VEGF levels were unaffected by neoadjuvant treatment but fell significantly on the first day after operation (652 *versus* 1057 pg/ml before operation; $P < 0.05$). No decrease occurred in control patients. VEGF levels had returned to preoperative levels by day 5. A similar postoperative rise in VEGF levels was seen in the control subjects (1194 pg/ml on day 5 *versus* 71 pg/ml before operation; $P = 0.001$). There was no correlation between VEGF level and response to treatment or tumour stage. VEGF levels had decreased significantly at 3 months following tumour resection (594 *versus* 1558 pg/ml on day 5; $P = 0.03$).

Conclusion: VEGF levels are raised in patients with oesophageal cancer and are unaltered by neoadjuvant treatment, suggesting an additional source other than tumour cells for this proangiogenic agent.

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Introduction

The growth of solid tumours beyond a size of 2 mm^3 cannot occur without the development of a new vasculature. Angiogenesis is required for tumour cell proliferation, extracellular matrix invasion and haematogenous spread[1]. In addition to nutrient supply and waste removal, tumour growth is facilitated by the paracrine stimulation of growth factors and matrix proteins produced by the new endothelium. The switch to the angiogenic phenotype appears to depend on the net balance between proangiogenic and antiangiogenic factors released by the tumour[2].

The importance of circulating angiogenic regulators has been emphasized by several authors[3,4]. O'Reilly *et al.*[4] have suggested that a primary tumour, by producing proangiogenic factors in excess of angiogenic inhibitors, can initiate its own neovascularization. The longer half-life of angiogenic inhibitors in the circulation, however, ensures that the balance of effects on tumour metastatic growth is inhibitory. Surgical extirpation of a primary tumour may remove the source of circulating angiogenic inhibitors. Two of the most potent, angiostatin and endostatin, are undetectable 5 days after tumour removal.

Raised levels of one of the most potent angiogenic mediators, vascular endothelial growth factor (VEGF), have been reported in the serum of patients with various types of cancer[5,6]. Raised pretreatment levels in small-cell lung carcinoma and non-Hodgkin's lymphoma have been associated with a poor outcome[7,8]. Patients with primary breast carcinoma also exhibit raised serum levels of VEGF[6,9]. The importance of VEGF in the progression of oesophageal carcinoma is well recognized. Tumours that stain positive for VEGF have a worse prognosis than those that do not[10–12]. Increased serum levels of VEGF in patients with oesophageal cancer have been reported previously[13].

The outlook for patients with oesophageal cancer is poor with fewer than 10 per cent surviving 5 years. A randomized controlled trial has demonstrated a survival advantage for patients treated with preoperative chemoradiotherapy (multimodal therapy)[14]. Neoadjuvant therapy results in a 20–40 per cent complete pathological response rate and treatment response is the best prognostic indicator, with the majority of complete responders achieving cure[14,15].

It was hypothesized that serum VEGF levels would be raised in patients with cancer of the oesophagus but would fall during treatment with chemoradiotherapy as malignant cells were eradicated. The level of VEGF in the serum of patients with oesophageal carcinoma was measured before treatment, during chemoradiotherapy and after surgery.

Patients and methods

Study groups

Forty-four patients diagnosed with oesophageal carcinoma, both squamous cell ($n = 20$) and adenocarcinoma ($n = 24$), were studied. There were 33 men and 11 women. All were treated with a standard regimen of neoadjuvant chemoradiotherapy followed by surgery[14]. Briefly, this consisted of two courses of 5-fluorouracil and cisplatin chemotherapy and 40 Gy radiotherapy before surgery. Patients underwent surgery after week 8. None of the patients underwent a palliative resection. The operative approaches used were abdomen and left chest ($n = 18$), Lewis–Tanner ($n = 16$) and three stage ($n = 10$). At the time of surgery seven patients were stage 0, i.e. had demonstrated a complete pathological response to treatment. The remainder demonstrated an incomplete response to treatment; nine patients were stage IIa, 13 stage IIb and 15 stage III.

Twenty patients who underwent surgery for non-neoplastic conditions and who had no previous history of malignancy acted as age- and sex-matched controls. The procedures concerned were thoracotomy and blebectomy ($n = 2$), splenectomy ($n = 2$), abdominal aortic aneurysm repair ($n = 5$), open cholecystectomy ($n = 3$), sigmoid colectomy for diverticular disease ($n = 5$) and open Nissen fundoplication ($n = 3$).

Venous assays

Peripheral venous blood was sampled at the time of diagnosis. Further samples were drawn within 24 h of completion of the first week of chemoradiotherapy and within 24 h of completion of the second course of chemotherapy at the end of week 6. Samples were also taken before operation and on days 1, 3 and 5 after operation. A final sample was taken 3 months after surgery in patients who had oesophageal cancer. Samples were centrifuged at 2000 r.p.m. for 30 min and the serum was separated, filtered and stored at –80°C. The samples were later assayed in batches for VEGF in duplicate using commercially available enzyme-linked immunosorbent assay kits (Quantikine™; R & D Systems, Minneapolis, Minnesota, USA).

Statistical analysis

Values are given as mean(s.e.m.). Data were analysed using an Apple MacIntosh computer (Apple Computer Inc., Cupertino, California, USA), using DataDesk™ version 4·1 software (Data Descriptions Inc., Ithaca, New York, USA). Correlation was established using the Pearson product moment correlation test, and paired and unpaired *t* tests were used to compare data between groups. Data were taken to be significant when $P < 0{\cdot}05$.

Results

Serum VEGF levels were raised in patients with oesophageal cancer compared with age-matched controls (mean (s.e.m.) 1157(104) (range 436–2350) *versus* 247(36) (range 52–538) pg/ml; $P < 0{\cdot}01$, unpaired *t* test). The 95th percentile of VEGF levels in the control group (391 pg/ml) was taken as the upper limit of normal. Forty-two of 44 patients with oesophageal cancer had serum VEGF levels in excess of this value.

Serum VEGF levels were raised regardless of stage: 1039(92) pg/ml in those demonstrating a complete pathological response, 986(27) pg/ml in those with stage IIa disease, 1163(72) pg/ml in those with stage IIb and 1244(107) pg/ml in patients with stage III carcinoma.

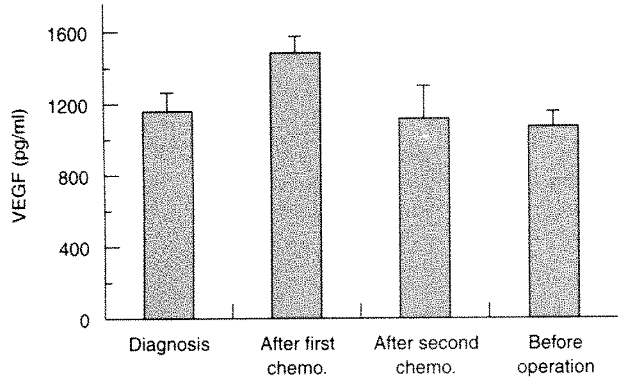

Fig. 1 Mean(s.e.m.) serum vascular endothelial growth factor (VEGF) levels during neoadjuvant chemoradiotherapy (chemo.)

There was no significant difference between the stages in terms of VEGF level.

Serum VEGF levels were unaffected by preoperative chemoradiotherapy; values remained high throughout the course of treatment (*Fig. 1*). Mean values were 1157(104) pg/ml at the time of diagnosis, 1473(82) pg/ml at the end of the first week of the neoadjuvant regimen, 1108(185) pg/ml following the second course of chemotherapy in week 6 and 1057(96) pg/ml immediately before operation.

A significant decrease in VEGF levels was seen on the first day after operation in patients with oesophageal carcinoma (652(48) *versus* 1057(96) pg/ml before operation; $P < 0{\cdot}05$, paired t test). A similar decline was not observed in control patients. VEGF levels in the oesophageal cancer group began to rise again by the third day after operation and had returned to pretreatment levels by day 5 (1558(127) pg/ml on day 5 after operation *versus* 652(48) pg/ml on day 1; $P < 0{\cdot}001$, paired t test). A similar rise in serum VEGF levels in the postoperative period was seen in control patients who underwent surgery for non-malignant disease (1194(146) pg/ml on day 5 *versus* 71(12) pg/ml before operation; $P = 0{\cdot}001$) (*Fig. 2*).

VEGF levels were significantly reduced at 3 months after surgery (594(160) pg/ml at 3 months *versus* 1558(227) pg/ml on day 5 after operation; $P = 0{\cdot}03$, paired t test). The difference between the value obtained 3 months after surgery and the preoperative level (1057(96) pg/ml) was also significant ($P < 0{\cdot}05$, paired t test) (*Fig. 2*).

Discussion

Raised VEGF levels in the serum of patients with oesophageal carcinoma have been reported previously by Linder *et al.*[13]. Several studies have identified VEGF in the biological fluids of patients with cancer, such as pleural and peritoneal effusions[16,17]. Raised VEGF levels have been reported in the serum of patients with ovarian[18], colorectal[19] and breast[9] carcinoma. Landriscina and colleagues[20] have reported raised levels of VEGF in the mesenteric blood of patients with colorectal cancer compared with peripheral venous blood samples in both tumour-bearing patients and healthy volunteers. Increased serum VEGF levels have been associated with a short tumour-volume doubling time in advanced colorectal carcinoma[21]. High levels of VEGF in serum taken immediately before treatment in patients with either small-cell lung carcinoma or non-Hodgkins lymphoma have been shown to be associated with an unfavourable outcome[8].

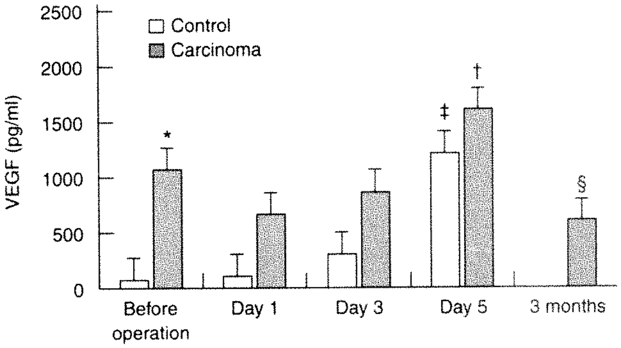

Fig. 2 Effect of surgery on mean(s.e.m.) serum vascular endothelial growth factor (VEGF) levels. $^*P < 0{\cdot}05$ patients with carcinoma before surgery *versus* patients with carcinoma on day 1 after operation, $^\dagger P < 0{\cdot}001$ *versus* patients with carcinoma on day 1 after operation, $^\ddagger P = 0{\cdot}001$ *versus* controls before operation, $^\S P < 0{\cdot}05$ *versus* patients with carcinoma before operation and $P = 0{\cdot}03$ at day 5 after operation (paired t test)

In the present study, there was no correlation between stage of tumour and VEGF level; raised levels were observed at all stages, including those in patients who demonstrated a complete pathological response. Yamamoto *et al.*[6] found notably higher VEGF levels with advanced disease stage. VEGF concentrations in tumour, mesenteric blood and peripheral blood showed a direct correlation with tumour stage in colorectal cancer[19,20].

The failure of VEGF levels to return to normal values during or after neoadjuvant therapy was unexpected. The raised levels seen in patients who had a complete pathological response were particularly surprising. These results suggest that the VEGF identified in the serum of these patients is not secreted by tumour cells alone. It has been suggested previously that the lack of difference between VEGF levels between various tumour types may indicate that host characteristics prevail on the tumour cell phenotype in determining the extent of angiogenesis[22]. Others have reported a decrease in serum VEGF levels following chemotherapy for gastric cancer, although not in patients who had progressive disease following treatment[23].

Several studies have demonstrated that removal of a primary colorectal adenocarcinoma decreased serum levels of basic fibroblast growth factor and VEGF, suggesting that the source of both angiogenic factors is present in the tumour tissue[19,22]. Similar observations have been made in relation to VEGF in breast cancer[6] and in the present study in patients undergoing surgery for carcinoma of the oesophagus. The failure of neoadjuvant therapy to reduce VEGF levels may be because other VEGF-producing cells contribute to the tumour bulk. Tumour-associated macrophages are removed at the time of tumour excision but remain largely unaffected by neoadjuvant treatment. The importance of tumour-associated macrophages as a stimulator of tumour angiogenesis has recently been identified[24]. Macrophages are potent producers of VEGF[16,25,26] and play a significant role in the angiogenic activity of breast carcinoma. Macrophage production of VEGF is upregulated by both hypoxia and transforming growth factor β1, both of which are present in the tumour environment[27].

Other possibilities are that the multimodality therapeutic regimen might be stimulating the production of VEGF, or that the raised serum VEGF levels may result from tumour cell lysis (and release of vascular growth factors)[28]. Alternatively, the persistently raised level of VEGF may be a reflection of a lack of sensitivity of the tumour to the treatment regimen. This is unlikely as all the tumours treated in this study demonstrated some degree of histological response to therapy.

VEGF levels fell dramatically by the first day after operation in patients with oesophageal cancer. This was not observed in the control patients, suggesting that the sudden decrease is due to the removal of the tumour, rather than any dilutional effect occurring as part of the stress response to surgery. VEGF levels rose sharply thereafter in the postoperative period. It is unclear whether this rise reflects a further and different source of secretion. Nissen *et al.*[29] found that VEGF was the significant angiogenic growth factor in wound healing from day 3 onwards. Surgery appears to be associated with increased VEGF levels, most probably due to a 'spillover' from the healing wound. The reduction in VEGF levels seen at 3 months would appear to substantiate this theory. This increase could be suppressed or modulated by antiangiogenic agents. This may be exploited as a potential further adjuvant approach to metastatic disease control.

Regardless of source, the raised VEGF levels seen in the perioperative period are a potential cause for concern as they may stimulate micrometastatic tumour growth. Micrometastases have been identified in the rib bone marrow of 88 per cent of patients with gastro-oesophageal carcinoma[30]. High serum VEGF levels have been shown to lead to an increase in the growth of micrometastases in a murine lung cancer model[31]. The enhancement of metastatic growth permitted by the removal of antiangiogenic agents secreted by the primary tumour could be further augmented by a rise in circulating VEGF levels in the postoperative period.

In conclusion, neoadjuvant chemoradiotherapy does not reduce serum VEGF levels in patients with oesophageal carcinoma. Surgery is associated with raised VEGF levels. This failure of chemoradiation to address the angiogenic component of tumour growth may provide an explanation for the treatment failures seen with this regimen and may offer a new avenue in the search for methods of improving the survival figures for this disease.

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Original article

Effect of oesophagectomy on monocyte-induced apoptosis of peripheral blood T lymphocytes

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Background: Surgical stress has been reported to induce immunosuppression. The mechanisms giving rise to T-cell dysfunction following surgery are still unclear. The cellular mechanisms behind T-cell dysfunction following surgery were investigated, based on the induction of T-cell apoptosis and downregulation of T-cell signalling molecules.

Methods: Peripheral blood T cells were collected and separated before and after surgery in patients who had oesophagectomy, gastrectomy or cholecystectomy, and studied for their ability to produce cytokines, the induction of T-cell apoptosis with terminal deoxynucleotidyl transferase-mediated dUPT-biotin nick end labelling methods, and the expression of T-cell signalling zeta (TCR ζ) molecules with intracellular staining.

Results: The increased degree of T-cell apoptosis, downregulation of TCR ζ molecules and impaired cytokine production of T cells were significant on days 1 and 3 after operation in patients who had oesophagectomy, but not after gastrectomy or cholecystectomy. A higher level of T-cell apoptosis was observed in the co-culture with postoperative monocytes than with preoperative monocytes.

Conclusion: Peripheral blood T cells obtained after oesophagectomy underwent apoptosis that correlated with the downregulation of TCR ζ molecules. Postoperative monocytes induced by surgical stress were able to mediate the T-cell apoptosis.

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Introduction

Experimental and clinical studies have demonstrated that the stress of surgery can result in impaired immune function, expressed as a decreased number of lymphocytes, reduced proliferative function of lymphocytes, depressed neutrophil function, impaired immunoglobulin production and a change in monocyte phenotype[1–5]. Immunocompromise following surgery induces vulnerability to bacterial, viral and fungal infections[2]. Furthermore, T-cell dysfunction can facilitate the growth of metastatic tumours as well as any residual tumour, since T cells play an important role in the elimination of tumour cells[6].

The decrease in the number of lymphocytes following surgery has been reported to be caused by increased serum levels of cortisol[7]. There may also be a shift to greater suppressor T-cell activity following surgery[8]. Similarly, there is decreased interleukin (IL) 2 activity in patients undergoing surgery[9], and surgical stress induces Fas-mediated apoptosis in circulating lymphocytes[10]. However, the cellular mechanism behind immunosuppression, in particular T-cell dysfunction induced by surgical stress, is still unclear. Recently, the authors reported one possible mechanism of T-cell dysfunction following surgery: postoperative monocytes induced by surgical stress cause a decreased expression of T-cell signalling zeta (TCR ζ) molecules in peripheral blood T cells. TCR ζ molecules are involved in signal transduction and the subsequent activation of T cells[11].

In the present study, the degree of T-cell apoptosis, the expression of T-cell signalling molecules and inducible tumour necrosis factor (TNF) α production from T cells were evaluated following surgery in order to analyse the cellular mechanism behind T-cell dysfunction induced by surgical stress.

Patients and methods

Patients

The study included 19 patients with oesophageal cancer, 26 patients with gastric cancer and ten patients with gallstones

Table 1 Patient characteristics

	Oesophagectomy ($n = 19$)	Gastrectomy ($n = 26$)	Laparoscopic cholecystectomy ($n = 10$)
Age (years)	69(6)	64(7)	58(10)
Stage*			
I	8	10	
II	5	7	
III	5	4	
IV	1	5	
Intraoperative blood loss (ml)	526(109)	354(99)	10(4)
Duration of surgery (min)	511(125)	301(45)	121(71)
APACHE II score†	7·1(1·1)	5·2(0·9)	3·1(1·1)

Values are mean(s.d.). *Japanese Classification of Gastric Carcinoma[23] and Guidelines for the Clinical and Pathological Studies on Carcinoma of the Esophagus (8th edition)[24]. †Acute Physiology and Chronic Health Evaluation (APACHE) II score was evaluated on day 1 after operation

who underwent surgery at the Yamanashi Medical University Hospital. Patients with oesophageal cancer underwent transthoracic oesophagectomy and reconstruction with a gastric tube. Patients with gastric cancer underwent distal or total gastrectomy. Patients with gallstones had laparoscopic cholecystectomy. The patient characteristics are shown in *Table 1*. Patients did not receive chemotherapy or radiotherapy during this study. No patient had any postoperative complications. Informed consent for blood sampling was obtained from all individuals.

Preparation of T cells

Peripheral blood samples were obtained by venous puncture before operation, and on days 1, 3 and 7 after surgery. Peripheral blood lymphocytes (PBLs) were separated by centrifugation on a Ficoll (Pharmacia, Uppsala, Sweden) gradient. Aliquots of the PBLs were used for TCR ζ staining (1×10^6) and a cytokine production assay (5×10^5). Aliquots of the PBLs (2×10^7) taken before and on day 1 after operation were frozen in 10 per cent dimethylsulphoxide (Sigma Chemical, St Louis, Missouri, USA) + 45 per cent fetal calf serum (FCS) for monocyte co-culture experiments.

To purify T cells, monocytes were removed from PBLs (1×10^7) by adherence to FCS-coated tissue-culture grade plastic (Coster, Cambridge, Massachusetts, USA) for 1·5 h at 37°C. Thereafter, the remaining cells were incubated in the presence of anti-CD16 and anti-CD19 monoclonal antibodies (Mabs) (10 µg/ml; Dako, Carpinteria, California, USA) for 30 min at 0°C for negative selection of T cells. The cells were then washed and incubated with magnetic beads coated with goat antimouse immunoglobulins (PerSeptive Diagnostics, Cambridge, Massachusetts, USA) for 30 min at 0°C. The negatively selected T cells were primarily CD3+ cells (94 per cent), as determined by flow cytometry. The negatively selected T cells were incubated in AIM-V (Gibco, Grand Island, New York, USA) for 20 h, and then the cells were subjected to TUNEL assay to detect T-cell apoptosis.

Co-culture of T cells with preoperative or postoperative monocytes

PBLs (2×10^7) from samples taken from the same patient before and 1 day after operation were thawed at the same time. Monocytes and T cells were separated as described above. The preoperative T cells (5×10^5) were co-incubated with preoperative or postoperative monocyte samples (4×10^5), with or without anti-Fas blocking antibody ZB-4 (5 µg/ml; MBL, Nagoya, Japan) for 20 h. Thereafter, non-adherent cells were subjected to terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin nick end labelling (TUNEL) assay to detect T-cell apoptosis. To confirm the ability of ZB-4 antibody, Jurkat cells were treated with agonistic anti-Fas antibody (CH-11, 0·2 µg/ml; MBL) with or without anti-Fas blocking antibody ZB-4 under the conditions described above.

Expression of T-cell signalling zeta molecules

The expression of TCR ζ molecules was investigated by flow cytometric analysis of permeabilized cells as described previously[11,12]. Briefly, PBLs were fixed with 0·5 per cent formaldehyde (Sigma) in phosphate-buffered saline for 20 min on ice, and then permeabilized with digitonin (10 µg/ml; Sigma) for 5 min on ice. After this, the cells were incubated with a saturating concentration of anti-ζ Mab (TIA-2; Coulter, Hialeah, Florida, USA) specific for the intracellular part of the ζ chain or immunoglobulin G1 isotype control antibody, followed by staining with a rabbit antimouse–fluorescein isothiocyanate isomer (FITC) antibody. After blocking with normal mouse serum, cells were double-stained with phycoerythrin-conjugated Mabs to CD3 (Dakopatts, Glostrup, Denmark) and then subjected to flow cytometric analysis using a FACScan flow cytometer (Becton and Dickinson, Mountain View, California, USA). CD3+ cells were gated and measured for mean fluorescence intensity of ζ molecules.

Cytokine production assay

To induce cytokine production, PBLs (5×10^5 per ml) were incubated for 48 h in a 48-well plate (Coster) precoated with Mabs to CD3 (10 ng/ml final concentration; OKT-3). The supernatants were collected and stored at −70°C. The TNF-α content was determined by means of an enzyme-linked immunosorbent assay (Medgenix, Fleurus, Belgium).

Detection of apoptotic T cells by TUNEL assay

The TUNEL assay was performed to detect DNA fragmentation of T cells by using the MEBSTATIN Apoptosis kit (MBL). Briefly, cells were fixed with 4 per cent paraformaldehyde at 4°C for 30 min. After washing, cells were treated with protein kinase K at 37°C for 30 min and permeabilized with 0·5 per cent Tween 20. After washing, DNA nick and labelling were performed with a mixture of biotin-2′-deoxyuridine 5′-triphosphate and TdT solution for 1 h at 37°C. After this, the cells were incubated with an avidin–FITC reagent. After incubation, the cells were measured by flow cytometric analysis with the FACScan. Negative controls included cells incubated without TdT enzyme in the labelling buffer. To evaluate the assay reliability, control samples from healthy donors ($n = 6$) were tested individually at the same time points as those of the patients scheduled for surgery.

Statistical analysis

Differences between two groups were analysed by paired two-tailed Student's t test and analysis of variance followed by Bonferroni posthoc tests, and were considered significant if $P < 0{\cdot}05$.

Results

Expression of T-cell signalling zeta in peripheral blood T cells

The authors have already reported that the expression of TCR ζ molecules in PBLs of healthy donors was quantitatively stable at different time points, as shown by flow cytometric analysis[11]. Using this method, the TCR ζ levels of PBLs were measured in samples taken before operation and on days 1 and 7 after surgery. There was no significant difference in the preoperative levels of TCR ζ expression between the groups (*Table 2*). The TCR ζ levels on day 1 after oesophagectomy were significantly lower than preoperative values, whereas there were no significant differences in the TCR ζ levels before and after gastrectomy or laparoscopic cholecystectomy (*Table 2*). These results indicated that TCR ζ molecules were impaired following surgery in patients who had transthoracic oesophagectomy.

T-cell cytokine production

The TNF-α production of T cells stimulated with anti-CD3 Mab was assessed to evaluate T-cell function before and after operation (*Table 3*). Preoperative levels of TNF-α production from T cells were impaired in patients who underwent oesophagectomy compared with levels in those who had laparoscopic cholecystectomy. Furthermore,

Table 2 Postoperative changes of T-cell signalling zeta expression in T cells

	TCR ζ expression (MFI)		
	Preop.	Day 1 postop.	Day 7 postop.
Oesophagectomy ($n = 19$)	81(11)	59(13)*	75(15)
Gastrectomy ($n = 26$)	79(16)	70(15)	76(16)
Laparoscopic cholecystectomy ($n = 10$)	90(16)	88(16)	n.a.

Values are mean(s.d.) mean fluorescence intensity (MFI) of T-cell signalling zeta (TCR ζ) expression measured using flow cytometric analysis of permeabilized cells. Preop., before operation; postop., after operation; n.a., data not available. *$P < 0{\cdot}05$ *versus* preoperative value (Student's t test)

Table 3 Postoperative changes in cytokine production from T cells

	TNF-α expression (pg/ml)		
	Preop.	Day 1 postop.	Day 7 postop.
Oesophagectomy ($n = 19$)	321(96)*	253(49)	322(10)*
Gastrectomy ($n = 26$)	349(95)	311(99)	355(98)
Laparoscopic cholecystectomy ($n = 10$)	421(109)†	391(95)	n.a.

Values are mean(s.d.) tumour necrosis factor (TNF) α production from cells stimulated with anti-CD3 monoclonal antibody. Preop., before operation; postop., after operation; n.a., data not available. *$P < 0{\cdot}05$ *versus* day 1 after oesophagectomy; †$P < 0{\cdot}05$ *versus* before oeseophagectomy (Student's t test)

TNF-α production of T cells was impaired on day 1 after operation but was restored to the preoperative level on day 7 after oesophagectomy, paralleling levels of TCR ζ expression. In the gastrectomy and cholecystectomy groups, there was no significant difference between the preoperative and postoperative levels. These observations indicated that peripheral blood T cells were functionally impaired following oesophagectomy.

Apoptosis of peripheral blood T cells

There was no significant difference in the induction of apoptosis of T cells from healthy donors taken at the same time points as patients scheduled for surgery (*Fig. 1a*), nor in the induction of T-cell apoptosis among the various groups before operation (*Fig. 1a*). The induction of T-cell apoptosis was significantly higher after oesophagectomy than after gastrectomy or cholecystectomy on days 1 and 3 after operation. The percentage of T-cell apoptosis was highest on day 1 after oesophagectomy in all patients and gradually decreased to the preoperative level on day 7 (*Fig. 1b*). These results indicate that T cells from patients who had oesophagectomy were susceptible to apoptosis.

Monocyte-induced apoptosis of peripheral blood T cells

To analyse the cellular mechanisms of T-cell apoptosis, preoperative T cells were incubated with either preoperative monocytes or postoperative monocytes (*Fig. 2*). A higher level of T-cell apoptosis was observed in the co-culture with postoperative monocytes than with preoperative monocytes in patients who had oesophagectomy. There was no significant T-cell apoptosis in co-culture with preoperative or postoperative monocytes from patients who had gastrectomy (*Fig. 2b*) or cholecystectomy (data not shown). The T-cell apoptosis observed in the co-culture with postoperative monocytes in patients who had oesophagectomy was not significantly inhibited by anti-Fas blocking ZB-4 antibody (*Fig. 2a*). The ZB-4 antibody did inhibit Fas-mediated apoptosis of Jurkat cells induced by agonistic anti-Fas Ab (CH-11) (*Fig. 3*). These results indicated that the induced apoptosis observed in the co-culture with postoperative monocytes in patients who underwent oesophagectomy was not mediated predominantly by Fas–Fas ligand interaction.

Discussion

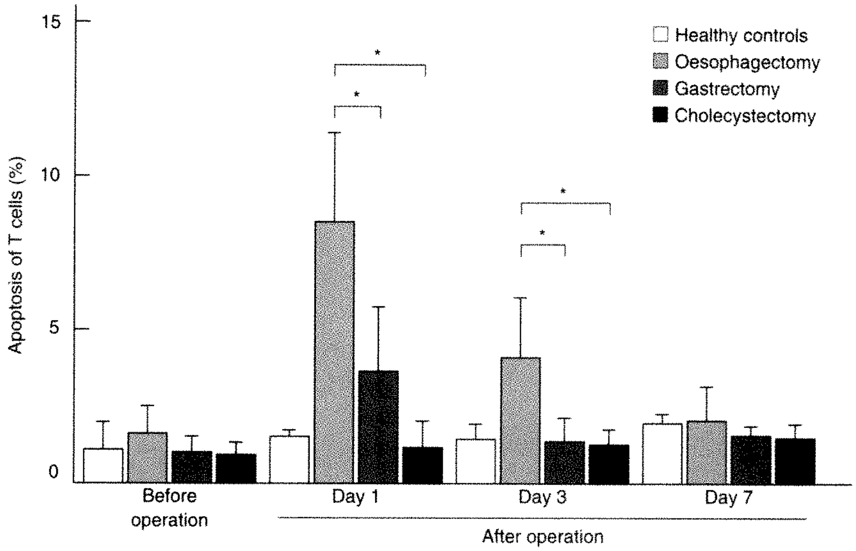
The present report contains several findings of relevance to postoperative T-cell dysfunction after oesophagectomy. First, peripheral blood T cells obtained after surgery, but not before surgery, underwent apoptosis. Second, postoperative monocytes induced by surgical stress were able to mediate the T-cell apoptosis.

In the present study, the induction of T-cell apoptosis following oesophagectomy coexisted with the downregulation of TCR ζ molecules on T cells, paralleling the T-cell dysfunction indicated by impaired cytokine production. The decreased expression of TCR ζ molecules following oesophagectomy confirmed the authors' previous finding that major surgical stress induces downregulation of TCR ζ molecules in T cells[11]. The cytoplasmic domain of TCR ζ molecules is involved in the signal transduction and activation of T cells, indicating that TCR ζ molecules are important for T-cell function[13]. Thus, downregulation of TCR ζ molecules is one of the possible mechanisms of postoperative T-cell dysfunction. The observation that T cells obtained after (but not before) surgery underwent apoptosis partly confirms a previous report that the apoptosis of circulating lymphocytes is induced by surgical stress[10]. However, the authors did not measure the apoptosis of the T-cell subpopulation, but rather the apoptosis of all lymphocytes[10]. The present study focused on T cells by negative selection of PBLs in order to clarify the T-cell dysfunction related to surgical stress.

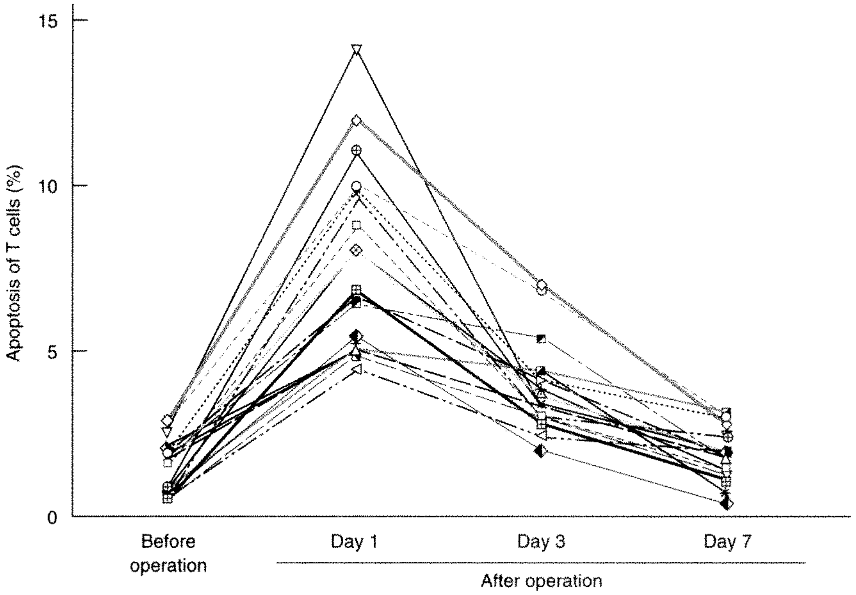
It has been shown recently that activated caspase, which was induced by apoptotic signals, directly degraded TCR ζ molecules in T cells[14]. This may explain the observation in the present study that the induction of T-cell apoptosis following surgery coexisted with the downregulation of TCR ζ molecules in T cells. It is speculated that activated caspase in T cells induced by apoptotic signals related to surgical stress might degrade TCR ζ molecules in T cells. Further studies are required to address this point.

With respect to the cellular mechanisms of T-cell apoptosis following surgery, a higher level of T-cell apoptosis was observed in the co-culture with postoperative monocytes induced by surgical stress than with preoperative monocytes. In general, resting peripheral blood T cells are resistant to Fas-mediated apoptosis[15]. However, it is also known that freshly isolated peripheral blood T cells are rapidly induced to undergo apoptosis when cultured with phorbol 12-myristate 13-acetate-activated monocytes[16]. There is increasing evidence that this monocyte-dependent T-cell apoptosis plays an important role in the control of T-cell apoptosis[17]. A previous study based on the analysis of phenotype and respiratory burst capacity in monocytes indicated that postoperative monocytes from patients who had oesophagectomy were strongly activated[5]. It is possible that postoperative monocytes, which were activated to a greater extent, induced peripheral T-cell apoptosis.

Oka *et al.*[10] reported that the apoptosis of peripheral lymphocytes following surgery was mediated by Fas.



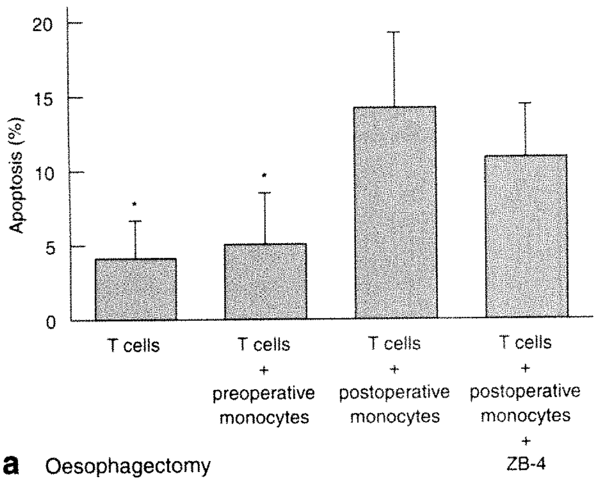
a T-cell apoptosis



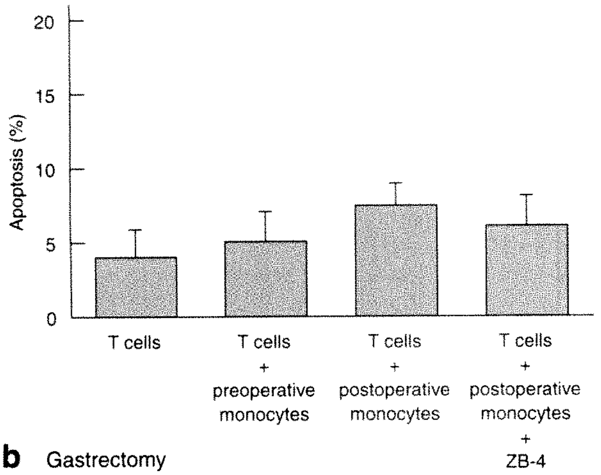
b T-cell apoptosis after oesophagectomy

Fig. 1 Apoptosis of peripheral blood T cells induced by surgery. The induction of T-cell apoptosis was determined by TUNEL methods before operation and 1, 3 and 7 days after oesophagectomy (n = 19), gastrectomy (n = 26) and cholecystectomy (n = 10), and at equivalent time points in healthy controls (n = 6). Mean(s.d.) values (**a**) and perioperative changes for individual patients who had oesophagectomy (**b**) are shown. $^*P < 0{\cdot}05$ (Student's t test)

However, the present study showed that T-cell apoptosis was not mediated predominantly by Fas–Fas ligand interaction, since this apoptosis was not significantly inhibited by anti-Fas blocking antibody, when T cells were co-cultured with postoperative monocytes. It has been shown that T-cell apoptosis requires a Fas-dependent[18] and



a Oesophagectomy



b Gastrectomy

Fig. 2 Apoptosis of peripheral blood T cells induced by postoperative monocytes in patients who had oesophagectomy (**a**) or gastrectomy (**b**). Values are mean(s.d.). $^*P < 0.05$ *versus* T cells + postoperative monocytes (Student's *t* test)

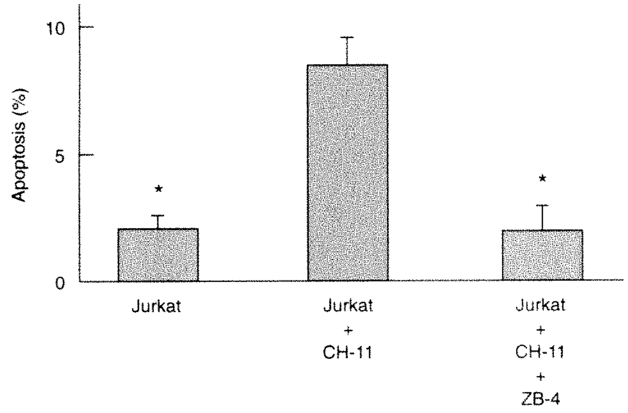


Fig. 3 Apoptosis of Jurkat cells induced by agonistic anti-Fas antibody (CH-11) is inhibited by ZB-4. Values are mean(s.d.). $^*P < 0.05$ *versus* Jurkat + CH-11 (Student's *t* test)

a Fas-independent[19] pathway. Monocyte-dependent T-cell apoptosis also appears to involve monocyte-derived reactive oxygen metabolites[16].

It has been reported that the severity of surgery affects the degree of immune alteration[20]. Lennard *et al.*[1] reported that major surgery produces a greater reduction in the absolute number of helper T cells than minor surgery. Similarly, there is decreased IL-2 activity of T cells in patients undergoing major surgery[9]. The recovery time necessary to restore normal immune function also reflects the magnitude of surgical damage[21]. In the present study, T-cell dysfunction related to apoptosis and decreased expression of TCR ζ molecules was seen in patients who had oesophagectomy, but not in those who underwent gastrectomy or cholecystectomy. Transthoracic oesophagectomy requires a cervical, thoracic and abdominal approach, the manipulation of several organs and prolonged surgery. Postoperative monocytes in patients undergoing oesophagectomy are more strongly activated than those in patients who have gastrectomy[5]. Serum IL-6 levels were also higher after oesophagectomy than gastrectomy[22]. Thus, it is likely that the difference in T-cell status between the different groups reflects the degree of surgical stress.

In conclusion, the peripheral blood T cells obtained from patients after oesophagectomy underwent apoptosis and were functionally impaired. Furthermore, postoperative monocytes induced by surgical stress were able to mediate the T-cell apoptosis. A better understanding of the effect of surgical stress on T-cell function may lead to the development of treatments aimed at normalizing the immune system after operation. In particular, the maintenance of T-cell function may be important after surgical treatment for cancer because T-cell-mediated immunity plays a central role in tumour immunology.

Acknowledgements

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Original article

Role of fundoplication in patient symptomatology after laparoscopic antireflux surgery

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Background: Symptoms following antireflux surgery are often seen as unavoidable sequelae of the operation. The aims were to determine the frequency of new adverse sequelae following antireflux surgery and the preoperative incidence of similar symptoms.
Methods: Patients undergoing fundoplication underwent prospective assessment of symptoms using a structured interview before and 6 months after surgery. In addition to the presence or absence of symptoms, Visick scores, visual analogue scales and a composite dysphagia score were used.
Results: Some 312 patients were evaluated. Antireflux surgery significantly diminished the symptoms of heartburn, epigastric pain, regurgitation, bloating, odynophagia, nausea, vomiting, diet restriction, nocturnal coughing and wheezing. In contrast, there was a significant increase in inability to belch, diarrhoea and increased passage of flatus. The symptoms of dysphagia, postprandial fullness or early satiety and anorexia were not significantly altered by antireflux surgery. There was, however, a group of patients who experienced new or worsened dysphagia after surgery and were more likely to do so if they had no dysphagia before surgery (31 per cent) than if dysphagia was present before surgery (19 per cent). Some 93 per cent of patients were satisfied with the overall outcome of the operation.
Conclusion: The majority of patients undergoing laparoscopic fundoplication for gastro-oesophageal reflux derive symptomatic benefit and are satisfied with the outcome. Many of the so-called postfundoplication sequelae are present before surgery in many patients. Overall, antireflux surgery does not lead to increased dysphagia or bloating.

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Introduction

Laparoscopic antireflux surgery is now a routine procedure undertaken for the relief of symptoms or the avoidance of long-term medication in patients with moderate to severe gastro-oesophageal reflux disease. While the majority of patients derive symptomatic benefit from such surgery, certain controversies still exist. Some patients are reported to suffer a variety of symptoms following antireflux surgery, in particular difficulty in swallowing, gas bloat and postprandial fullness or early satiety[1–13]. Such symptoms are seen as marring an otherwise highly effective treatment for gastro-oesophageal reflux disease. Furthermore, a recently reported randomized trial of open *versus* laparoscopic Nissen fundoplication was terminated prematurely owing to excessive adverse events (mainly postoperative dysphagia) in the laparoscopic arm of the study[14].

The presence of a variety of symptoms, some typical and others 'atypical' of gastro-oesophageal reflux disease, has been established in a number of patient groups and population surveys[15,16]. While heartburn and regurgitation are usually indicative of gastro-oesophageal reflux disease, other symptoms such as epigastric pain, difficulty in swallowing, nausea and vomiting are less so. If such symptoms are not related to the patient's reflux, it is likely that they will persist after antireflux surgery. Few detailed investigations of symptoms before and after antireflux surgery have been reported. The aim of this study was to evaluate symptoms before and 6 months after laparoscopic antireflux surgery, with particular emphasis on dysphagia.

Patients and methods

Patients selected for this study had previously been recruited to one of three prospective randomized trials.

All patients underwent a detailed standardized preoperative and postoperative symptom assessment; a common assessment protocol was used for all three trials. The trials were Nissen fundoplication with *versus* without division of short gastric vessels[10], Nissen fundoplication with anterior *versus* posterior hiatal repair, and Nissen fundoplication *versus* 180° anterior partial fundoplication[1]. Patients were not included in this study if they required a concurrent abdominal procedure with the fundoplication. All patients underwent preoperative investigation with oesophageal manometry and endoscopy. Twenty-four-hour pH monitoring was performed in patients who did not have unequivocal reflux disease demonstrated by endoscopy and only patients with objective evidence of reflux were included. Ethics committee approval had been given for all three trials and informed consent was obtained from each patient.

Patients had a structured interview with an independent scientist at assessment before operation and 6 months after surgery. The following symptoms were sought: heartburn, epigastric pain, regurgitation, difficulty swallowing lumpy solids, soft solids and liquids, painful swallowing, postprandial fullness or early satiety, inability to belch, bloating, poor appetite, nausea, vomiting, nocturnal coughing and wheezing. The ability to relieve bloating and whether a normal diet was consumed were also determined. Patients were asked about any increase in the passage of flatus or diarrhoea following surgery.

Heartburn and dysphagia for both liquids and solids were assessed by means of a visual analogue scale (0, no symptoms; 10, severe symptoms). In addition, a previously validated dysphagia score[17] (0, no dysphagia; 45, severe dysphagia), which combines information about difficulty in swallowing nine types of solid and liquid, was determined.

Overall outcome was determined using three scales that have been described previously[1,10]. Patients ranked the outcome of surgery using a modified Visick grading[1,10]. Patients also scored the outcome as excellent (complete recovery), good (major improvement with minor problems), fair (major improvement but still significant problems or adverse effects) or poor (minor or no improvement or deterioration). An overall assessment of satisfaction with the operative outcome was also scored by a visual analogue score (0–10). Finally, the patients were asked, given their knowledge of the outcome of the operation, whether they would still choose to have the procedure if they could go back in time and decide again.

All data were entered into a computerized database (Filemaker Pro™ version 4.0; Claris, Santa Clara, California, USA) and analysed using a commercially available statistical package (InStat™ version 2.10; Graphpad Software, San Diego, California, USA). Two-sided Fisher's exact test was used to determine the significance of 2 × 2 contingency tables with statistical significance accepted at $P < 0·05$.

Results

Three hundred and twelve patients (62 per cent male) were studied prospectively. The median age was 44 (range 17–74) years. Symptoms of reflux had been present for a median of 6 years (range 6 months to 50 years) before surgery. A Nissen fundoplication was performed in 258 patients, and short gastric vessels were divided in 52 of these. The remaining 54 patients underwent a 180° anterior fundoplication without division of the short gastric vessels. Repair of the hiatus was routine practice although it was not performed in seven patients (2 per cent), mainly because of difficulties with exposure. The variation in surgical procedures reflected the randomization protocol under investigation at the time. Ten operations (3 per cent) were converted to an open procedure.

Using the modified Visick grading for symptoms, the median score before operation was 4 (range 1–4) (*Table 1*). Six months after surgery, the median score was 2 (range 1–5) (*Table 1*). The median heartburn score was 5 (range 0–10) before and 0 (range 0–10) 6 months after operation. Six months after surgery, nine patients (3 per cent) were taking proton pump inhibitors, four (1 per cent) were taking histamine receptor antagonists, eight (3 per cent) were using antacids and one patient was taking a prokinetic agent. The medications were usually instigated either by the patient or the general practitioner, and few were taken because of objective evidence of recurrent reflux.

Table 2 shows the presence of symptoms relating to gastro-oesophageal reflux disease before and 6 months after surgery. Antireflux surgery significantly diminished the symptoms of heartburn, epigastric pain, regurgitation, odynophagia, epigastric bloating, nausea, vomiting, diet restriction, nocturnal coughing and wheezing. In contrast, antireflux surgery was followed by a significant increase in

Table 1 Modified Visick grading of symptoms in 312 patients before and 6 months primary laparoscopic reflux surgery[1,10]

Modified Visick grading	Before operation	After operation
1	3 (1)	100 (34)
2	8 (3)	145 (49)
3	91 (31)	28 (10)
4	195 (66)	16 (5)
5	n.a.	5 (2)

Values in parentheses are percentages. n.a, Not applicable

Table 2 Presence of symptoms in 312 patients before and 6 months after primary laparoscopic reflux surgery

Symptom	Before operation	After operation	P^*
Heartburn	279 (89)	27 (9)	< 0·0001
Epigastric pain	220 (71)	126 (40)	< 0·0001
Regurgitation	257 (82)	23 (7)	< 0·0001
Dysphagia	102 (33)	114 (37)	0·35
Lumpy solids	99 (32)	111 (36)	0·45
Soft solids	27 (9)	19 (6)	0·28
Liquids	21 (7)	27 (9)	0·45
Odynophagia	116 (37)	15 (5)	< 0·0001
Post prandial fullness or early satiety	116 (37)	105 (34)	0·40
Epigastric bloating	159 (51)	97 (31)	< 0·0001
Inability to belch	50 (16)	102 (33)	< 0·0001
Anorexia	28 (9)	14 (4)	0·08
Nausea	84 (27)	21 (7)	< 0·0001
Vomiting	78 (25)	7 (2)	< 0·0001
Diet restriction	84 (27)	31 (10)	< 0·0001
Nocturnal coughing	129 (41)	33 (11)	< 0·0001
Nocturnal wheezing	55 (18)	23 (7)	0·002
Diarrhoea	1 (0)	14 (4)	0·0009
Increased flatus		104 (33)	
Wound pain		4 (1)	
Constipation		3 (1)	

Forty-seven patients (15 per cent) had none of these symptoms 6 months after operation. *Fisher's exact test

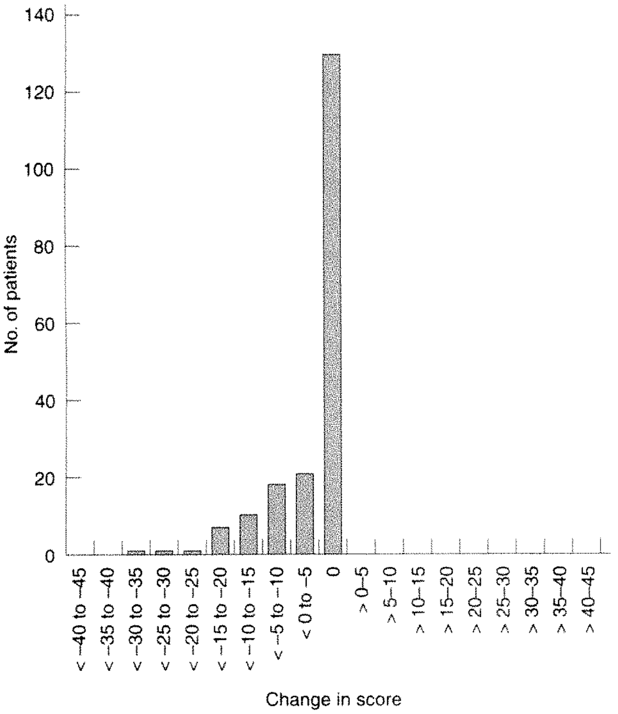

Fig. 1 Change in dysphagia score (0–45 composite score) 6 months after operation in 188 patients with no dysphagia before laparoscopic antireflux surgery (score 0). A positive change in score denotes an improvement in dysphagia

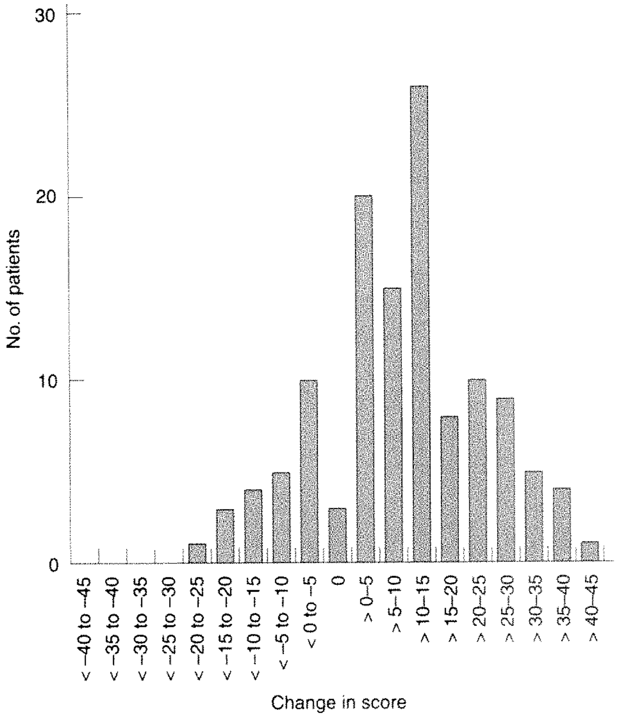

Fig. 2 Change in dysphagia score (0–45 composite score) 6 months after operation in 124 patients with dysphagia before laparoscopic antireflux surgery (score above 0). A positive change in score denotes an improvement in dysphagia

the symptoms of inability to belch, diarrhoea and increased passage of flatus. The symptoms of dysphagia, postprandial fullness or early satiety and anorexia were not significantly altered by antireflux surgery.

Before surgery, the median dysphagia score measured by a visual analogue scale was 0 (range 0–10) for liquids and 0 (range 0–10) for solids. Six months after surgery, the median (range) scores remained unchanged. However, with dysphagia for liquids, patient scores improved in 88 patients (28 per cent), were unchanged in 204 patients (65 per cent) and deteriorated after surgery in 20 patients (6 per cent). With dysphagia for solids, patient scores improved in 53 patients (17 per cent), were unchanged in 163 patients (52 per cent) and deteriorated after surgery in 96 patients (31 per cent).

The median value for the 0–45 composite dysphagia score was 0 (range 0–40) before surgery and 0 (range 0–45) 6 months after surgery. The dysphagia score improved in 98 patients (31 per cent), remained unchanged in 132 patients (42 per cent) and deteriorated after surgery in 82 patients (26 per cent). One hundred and eighty-eight patients (60 per cent) had no dysphagia (score 0) before surgery. Six months after surgery, 59 (31 per cent) of these patients noted varying degrees of dysphagia (*Fig. 1*). One hundred and twenty-four patients (40 per cent) had a dysphagia score above 0 before surgery. The dysphagia score improved in 98 patients (79 per cent), remained unchanged in three patients (2 per cent) and deteriorated after surgery in 23 patients (19 per cent) (*Fig. 2*). In 44 patients with dysphagia before surgery, the score fell to 0 (i.e. no dysphagia) at 6 months after surgery.

The median overall satisfaction score 6 months after surgery was 9 (range 0–10). One hundred and nine patients (37 per cent) rated the outcome as excellent, 160 patients (54 per cent) as good, 23 patients (8 per cent) as fair and five patients (2 per cent) as poor. Two hundred and ninety patients (93 per cent) said that they would have the procedure again knowing what the surgery involved and the outcome.

Discussion

This study demonstrates that the majority of patients undergoing laparoscopic fundoplication for gastro-oesophageal reflux derive symptomatic benefit and are satisfied with the outcome. Heartburn, epigastric pain and regurgitation are the dominant symptoms in most series of fundoplication for reflux disease. In the present study, the number of patients experiencing heartburn and regurgitation was reduced by an order of magnitude following fundoplication (*Table 2*). This absolute reduction in symptoms (as well as a reduction in intensity of symptoms in those still experiencing heartburn or regurgitation) is a consistent result in the literature[4,6–8,11–13,18].

Dysphagia following fundoplication is more controversial. One-third of patients in the present study reported varying degrees of dysphagia before surgery, consistent with other large series that have reported preoperative dysphagia in up to 54 per cent[2,5,8,9,11,13]. How the questions about dysphagia are asked, who asks the questions and the scoring system applied can all influence the apparent incidence of the symptom[10]. An attempt was made to minimize such variability in the present study. In this study, 33 per cent of patients reported difficulty before surgery to the question 'Do you have difficulty swallowing lumpy solids, soft solids and/or liquids?' However, on more detailed questioning using the composite dysphagia score, 40 per cent of patients reported difficulty swallowing one or more of the index foodstuffs before surgery. Six months after fundoplication, a similar proportion of patients (37 per cent) reported dysphagia to lumpy solids, soft solids and/or liquids. On more detailed examination using the composite dysphagia score before and after fundoplication, about one-third of patients who reported no dysphagia before surgery (score 0), developed some degree of dysphagia following surgery (*Fig. 1*). Fortunately, most of this 'new' dysphagia was mild in nature. Of patients with dysphagia before surgery (score greater than 0), 79 per cent reported improvement in their dysphagia following surgery (the score fell to 0 in almost half of these), and only 19 per cent reported a deterioration in their dysphagia. In other words, in percentage terms, new or worsening dysphagia was more likely to occur in patients who had no dysphagia before operation. The reason for this is unclear but the observation that fundoplication improves oesophageal motor function in patients with existing dysmotility may partly explain this finding[5,19]. Some degree of dysphagia is very common in the first few weeks following laparoscopic fundoplication but this has usually improved by 6 months with further small improvement up to 1–2 years after surgery. Several reported audits of laparoscopic antireflux surgery are consistent with the findings of the present study in that new dysphagia following surgery can occur in up to 50 per cent of patients[2,5,8,9,11,13]. Furthermore, patients with dysphagia before surgery are more likely to have an improvement rather than a deterioration in their dysphagia following fundoplication[7,8,11,18,20].

Effective control of reflux by antireflux surgery is thought to lead to abdominal distension and the so-called 'gas bloat' syndrome, loss of the ability to belch. This study demonstrated a significant reduction in the number of patients experiencing bloating, no significant change in the number of patients experiencing postprandial fullness or early satiety and a significant doubling in the number of patients reporting an inability to belch following fundoplication. These findings would appear somewhat inconsistent with each other but the subjective nature of patients' reporting of symptoms is acknowledged. Furthermore, these symptoms are difficult to measure objectively and vary widely in incidence both before and after surgery. Reported ranges following surgery are 1·5–100 per cent of patients unable to belch and 13–67 per cent complaining of gas bloating[21].

There is increasing interest in quality of life assessment following surgical intervention. The present study has not used quality of life assessment tools. However, a number of scales were used to ascertain patient satisfaction with the procedure. Patient satisfaction was around 90 per cent in the present study, consistent with the literature[1,3,7,10,13,22]. Nevertheless, a small number of patients are not satisfied with their outcome and, indeed, a small proportion of these patients are worse off after surgical intervention. Further research is required to identify patients who do not seem to benefit from surgery in its current form and also to refine surgical techniques to minimize adverse outcome. Patient personality and expectation are recognized to contribute to outcome but, at present, such assessment is not used routinely to alter surgical decision making[23,24].

Laparoscopic fundoplication is now established as a safe surgical treatment for gastro-oesophageal reflux disease. Patients can be reassured that the majority of their symptoms will be improved or negated, but should be informed about potential problems with new or worsening dysphagia, inability to belch, diarrhoea and increased passage of flatus.

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Chronic pain and quality of life following open inguinal hernia repair

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Background: The aim was to determine the frequency and characteristics of chronic pain following open inguinal hernia repair and to identify risk factors for its development.

Methods: This was a questionnaire survey of a historical cohort of patients who underwent inguinal hernia surgery in Aberdeen. The sample comprised all patients ($n = 351$) who underwent surgery between January 1995 and December 1997, and who were alive and resident in Grampian in October 1999. Outcome measures included self-report of pain persisting for more than 3 months after operation. Pain was characterized by means of the McGill Pain Questionnaire, and quality of life was assessed with the Short Form 36 (SF-36).

Results: A total of 226 patients (64 per cent) completed the questionnaire, 67 (30 per cent) of whom reported chronic pain. Reported pain was predominantly neuropathic in character. Patients at increased risk of chronic pain were under 40 years old ($P < 0{\cdot}001$), had day-case surgery ($P = 0{\cdot}004$), had subsequent surgery on the same side ($P < 0{\cdot}005$) and recalled pain before operation ($P = 0{\cdot}005$). The SF-36 scores were significantly different in the social functioning, mental health and pain dimensions in patients with chronic pain.

Conclusion: Chronic pain occurred in 30 per cent of patients after open hernia repair, a higher frequency than has been reported previously. Several risk factors were identified and further prospective research is recommended.

Preliminary findings of this study were presented to the Surgical Audit Symposium of the Royal College of Surgeons of Edinburgh in Edinburgh, March 2000

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Introduction

Chronic pain following inguinal hernia repair is a recognized long-term complication, but is believed to be infrequent[1,2]. A recent Canadian study[3] challenged this view, reporting that 12 per cent of patients suffered moderate to severe pain 2 years after operation. The chronic pain was described by these patients as pulling, tearing and sharp; it was subsequently classified by the authors as somatic, neuropathic and visceral in character. A recent Danish study[4] addressed the issue of chronic pain 1 year after inguinal hernia repair. The aim of the present study was to estimate the frequency of chronic pain following inguinal hernia surgery, to describe its characteristics, to identify the factors that might increase the risk of chronic pain and to assess its impact on quality of life.

Patients and methods

The study was a cohort-based follow-up of consecutive patients who underwent open operation for inguinal hernia in one surgical unit, under the care of three consultants. The International Association for the Study of Pain[5] definition of chronic pain (pain persisting beyond the normal tissue healing time assumed to be 3 months) was used as the primary outcome measure. The definition of chronic pain used in this study was also based upon three further criteria: the character, quality and location of pain. The character of pain was either neuropathic or non-neuropathic according to presence of numbness and sensations; the quality of pain was either sensory–discriminative, motivational-affective or cognitive-evaluative as classified by the McGill Pain Questionnaire; finally, the pain had to be adjacent to the area of operation.

The study sample size was based on an expected 70 per cent response rate, an estimated frequency of chronic pain from previous studies of 12 per cent and confidence interval (c.i.) of ± 2 per cent. The study population comprised all patients who underwent inguinal hernia surgery ($n = 423$) in one surgical unit between January 1995 and December 1997 identified from a prospective surgical database, the Expandable Medical Audit System (EMAS). This database held demographic and operative details for each patient, including surgical technique (suture or mesh), type of admission (day case or inpatient) and whether or not the operation was for primary or recurrent hernia. The hernia repair techniques employed were a Bassini repair (with division and resuture of the transversalis fasica), a rectus sheath flap or a Lichtenstein tension-free mesh repair.

Vital status and residence within the Grampian region was checked with the Community Health Index, subsequently reducing the sample size to 386 patients. A pilot study was undertaken on 35 patients, and following this the questionnaire was refined and the final survey was conducted in October 1999 on the remaining 351 patients. The study was approved by the Grampian Research Ethics Committee.

Questionnaire

The study questionnaire was based on questionnaires used in previous studies of pain after operation[6] and included questions on demography, such as marital, educational and employment status, job description and housing. Questions were included on preoperative pain. Standard questions were included from the McGill Pain Questionnaire[7], the University of California and San Francisco (UCSF) Pain Service patient questionnaire[8] and the Short Form 36 (SF-36) questionnaire. A body chart was included in the questionnaire where participants could mark the location of pain and use symbols to indicate its characteristics. Patients were also asked to report their current height and weight. Questionnaires were sent with a covering letter and a stamped addressed envelope, followed by two reminder letters at 3-week intervals if there was no response.

Statistical analysis

The statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) for Windows, version 9·01 (SPSS, Chicago, Illinois, USA). $P < 0.05$ was considered significant. χ^2 tests were used to examine associations between different variables and the presence of chronic pain; t tests were used to compare the means of certain characteristics between patients with and without chronic pain; and the Mann–Whitney U test was used to analyse ordinal variables. Logistic regression was done to estimate the strength of association between the variables. The SF-36 questionnaire was analysed using the standard SPSS syntax program. Responses to the SF-36 were summed to yield eight scores ranging from 0 (worst health possible) to 100 (best health possible). Three methods (Pain Rating Index using scale values, Pain Rating Index using the weighted ranking method, and the number of words chosen) were used to analyse the McGill Pain Questionnaire[9].

Results

A total of 292 (83 per cent) patients returned questionnaires after two reminder mailings. Of these, 226 questionnaires were fully completed, 64 (18 per cent) were returned blank and two (1 per cent) were incomplete. The following analysis is based on the 226 patients (64 per cent) who completed the questionnaire satisfactorily. Overall, the response rate increased with age and there was a better response from women (all 21 responded) than from the 271 men (82 per cent response rate). The majority of non-responders were men in the 40–60 years age range. The mean age of respondents was 61 years, compared with 50 years for non-respondents. There was no significant difference in response rate between consultant code or type of admission (day case, inpatient, emergency).

The median interval since the operation was 43 (range 21–57) months. Most patients (71 per cent) in the study group were married and 176 (78 per cent) were living in a family. A total of 101 patients (45 per cent) were working full or part time and 97 patients (43 per cent) were retired. Operative details were analysed from the surgical database; 168 patients (74 per cent) had one of the suture repairs and 58 (26 per cent) underwent mesh repair. The majority of patients (82 per cent) had surgery as inpatients, with 12 per cent having the operation as a day case.

Questionnaire results

Chronic pain lasting more than 3 months, consistent with the definition used in this study, was reported by 67 (30 (95 per cent c.i. 24–36) per cent) of the 226 patients. The frequency of chronic pain decreased with age: from 58 per cent in patients aged under 40 years to 14 per cent in those aged over 60 years. No differences were found in marital or household status between patients with or without chronic pain, but employment status differed between the groups (*Table 1*). In those who reported chronic pain, the time of onset was variable and the frequency of the pain ranged from continuous to less than once a month. A variety of words was used to describe the pain; these included

Table 1 Demographic characteristics of patients with and without chronic pain after open inguinal hernia repair

	n	Chronic pain	No chronic pain	*P**
Age (years)				< 0·001
Less than 40	19	11 (58)	8 (42)	
40–60	82	33 (40)	49 (60)	
More than 60	118	16 (14)	102 (86)	
Not recorded	7			
Body mass index (kg/m^2)				0·341
Normal	66	16 (24)	50 (76)	
Overweight	109	31 (28)	78 (72)	
Obese	40	15 (38)	25 (62)	
Not recorded	11			
Employment status				< 0·001
Working (full or part time)	101	35 (35)	66 (65)	
Retired	97	14 (14)	83 (86)	
Unemployed or student	5	3 (60)	2 (40)	
Cannot work due to illness or disability	10	7 (70)	3 (30)	
Not recorded	13			

Values in parentheses are percentages. *χ^2 test

numbness, pins and needles, stabbing, burning and aching. Based on the study of verbal description of neuropathic pain by Boureau *et al.*[10], the description of pain by 31 patients (46 per cent) in this study was typically neuropathic in character. Fourteen patients (21 per cent) described non-neuropathic pain and 11 (16 per cent) used both neuropathic and non-neuropathic descriptors. Analysis of the McGill Pain Questionnaire revealed that the chronic pain reported by the majority of patients was sensory-discriminative in quality. The Pain Rating Index[11], using the scale values and weighted ranking method, was 13 and 10·9 respectively.

At the time of the survey 53 (79 per cent) of the 67 patients with chronic pain reported that they still suffered pain, 13 reported that the pain had disappeared on its own, and one response was not recorded. Pain was described as moderate to unbearable by 30 per cent of these patients. There was no association between the type of pain (neuropathic *versus* non-neuropathic) and the severity ($P = 0.47$). Pain was reported to be aggravated by straining, sudden movement, coughing and standing, and relieved by lying down and sitting. The majority of patients (80 per cent) reported pain in the area of the operation but ten (15 per cent) had pain in the front of the thigh. Twenty patients (30 per cent) reported testicular pain and 19 per cent that pain interfered with sexual activity. Sixteen patients (24 per cent) had used painkillers prescribed by general practitioners, seven (10 per cent) had purchased analgesics from the chemist and seven (10 per cent) had tried physiotherapy. All patients reported only mild pain relief from these interventions.

Quality of life

Analysis of the SF-36 revealed that there were significant differences between patients with and without chronic pain in three of eight health dimensions: social functioning, mental health and pain (*Table 2*). Pain was reported to have affected activities of daily living in the previous 6 months for up to 6 days in 40 patients (60 per cent) with pain, and for more than 1 month in six patients (9 per cent). Four patients (6 per cent) experienced an extreme change in their ability to take part in recreational or social activities, as well as with daily activities. Pain affected sleep in eight patients (12 per cent). Of 29 patients who commented on change in the intensity of pain, four reported that pain increased in intensity, 17 said that pain decreased and eight reported that the pain was variable.

Risk of developing chronic pain

Age was the strongest risk factor for developing chronic pain, decreasing from 58 per cent in patients aged under 40 years to 14 per cent in those over 60 years old ($P = 0.001$). There was a non-significant trend in increasing frequency of chronic pain with increasing body mass index (kg/m^2). Patients in full-time employment were more likely to suffer chronic pain than those who had retired ($P = 0.001$) (*Table 1*). Patients who underwent mesh repair reported more chronic pain than those who had suture repair, but this was not significant ($P = 0.08$). There was no association between chronic pain and grade of surgeon (senior *versus* middle grade; $P = 0.42$); however, day-case patients reported chronic pain more often than inpatients (54 *versus* 24 per cent; $P = 0·004$) (*Table 3*). The mean age of day-case patients was 53 years, compared with 62 years for inpatients, which may explain this difference. However, logistic regression revealed that the probability of developing chronic pain decreased by 5 per cent with each 1-year increase in age; the probability of developing chronic pain was 2·5 times higher in day-case patients, controlling for age. Patients who had subsequent repair of an ipsilateral recurrent hernia were more than four times as likely to develop chronic pain (odds ratio 4·54, $P = 0·005$). In addition, patients who recalled having preoperative pain developed chronic pain more frequently (odds ratio 3·53, $P = 0·005$).

Table 2 Comparison of Short Form 36 dimensions and pain scores in patients with and without chronic pain after open inguinal hernia repair

Health dimension	No. of patients	Pain score (mean rank)	*P**
Physical functioning			
No chronic pain	141 (72)	99·35	0·732
Chronic pain	55 (28)	96·31	
Social functioning			
No chronic pain	150 (72)	109·04	0·046
Chronic pain	58 (28)	92·77	
Role physical			
No chronic pain	141 (70)	102·56	0·371
Chronic pain	59 (30)	95·57	
Role emotional			
No chronic pain	144 (71)	102·53	0·588
Chronic pain	58 (29)	98·95	
Mental health			
No chronic pain	151 (72)	111·11	0·018
Chronic pain	58 (28)	89·10	
Energy/fatigue			
No chronic pain	149 (72)	108·57	0·078
Chronic pain	58 (28)	92·27	
Pain			
No chronic pain	147 (72)	114·68	< 0·001
Chronic pain	58 (28)	73·40	
General health perception			
No chronic pain	150 (72)	106·45	0·451
Chronic pain	58 (28)	99·46	

Values in parentheses are percentages. *Mann–Whitney *U* test

Discussion

Two recent studies have reported a higher frequency of chronic pain following inguinal hernia repair[3,4]. The present study confirms that chronic pain following open inguinal hernia surgery is commoner than hitherto reported. This may be due to the definition of chronic pain, differences in the methods of ascertainment or the age of the population studied. An internationally accepted standard definition of 'pain persisting beyond the normal tissue healing time assumed to be 3 months' was used in the present study[5]. A retrospective approach was employed in that patients were asked to report their experience of surgery conducted up to 5 years previously. Patients were asked to recall whether or not they had had pain before operation, and the reliability of this observation in a retrospective study is questionable. Despite these limitations, of patients who reported chronic pain, the majority (79 per cent) stated they still had pain at the time of survey.

There was a good overall response rate of 83 per cent to the questionnaire, but only 65 per cent were valid. The majority of non-responders were in the younger age group.

Table 3 Risk factors for developing chronic pain after open inguinal hernia repair

Risk factor	Chronic pain*	No chronic pain*	Odds ratio†	*P*‡
Type of admission				
Day case	13 (54)	11 (46)	3·72 (1·45–9·64)	0·004
Inpatient	47 (24)	148 (76)		
Preoperative pain				
Pain	50 (35)	95 (65)	3·53 (1·40–8·32)	0·005
No pain	7 (13)	47 (87)		
Surgery				
Subsequent operation	19 (40)	28 (60)	2·16 (1·03–4·52)	0·04
Initial operation only	39 (24)	124 (76)		
Same side				
Subsequent operation on same side	10 (59)	7 (41)	4·54 (1·47–14·35)	0·005
Initial operation only	39 (24)	124 (76)		
Opposite side				
Subsequent operation on opposite side	9 (30)	21 (70)	1·36 (0·53–3·46)	0·63
Initial operation only	39 (24)	124 (76)		

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡χ^2 test

Nevertheless, if all non-responders were pain-free, the frequency of chronic pain for the whole sample would still be 19 per cent (67 of 351), which remains higher than reported previously.

This study described the natural history and the extensive variation in onset, course, severity and quality of chronic pain after open inguinal hernia repair. Inclusion of the standard SF-36 questionnaire provided the opportunity to assess the general health of patients and the McGill questionnaire used in this study is a reliable and valid instrument for quantitative and qualitative assessment of pain reported by patients[7]. A recent prospective study of chronic pain was unable to differentiate between neuropathic and somatic pain[4]. The present findings suggest that the chronic pain was predominantly neuropathic in character.

This study also identified a number of risk factors associated with chronic pain after inguinal hernia repair: younger age, day-case surgery, presence of preoperative pain and operation for recurrent hernia. Younger patients could be more anxious to report pain or be more sensitive to nerve damage. Studies of chronic pain after other types of operation have also reported a higher frequency of chronic pain in younger patients[6]. Smith *et al.*[6] reported a higher prevalence of postmastectomy pain in young women. Day-case hernia surgery is often used for young patients; however, in spite of taking age into consideration, the risk of developing chronic pain remained higher in day-case patients. Further prospective studies are needed to determine whether the higher frequency of chronic pain in day-case patients is related to specific anaesthetic, operative or organizational factors. The higher frequency of pain reported by patients who had surgery for recurrent herniation is similar to that described by Callesen *et al.*[4] in 1999. This higher prevalence of chronic pain may be due to nerve entrapment in previous scar tissue[12]. The trend of more pain with increasing body mass could be associated with difficulty in identifying the ilioinguinal nerve. The high frequency of pain in patients who recalled having preoperative pain is also consistent with findings from other surgical pain studies[6].

Although not significant, a higher proportion of patients with chronic pain had undergone mesh repair. The increased surface area of the mesh might allow adherence of nerves or abrasion to account for an increased risk of neuropathic pain. Mesh repairs are generally considered to cause less early postoperative pain[13] and this observation, if confirmed, could have important implications.

Acknowledgements

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The Editors welcome topical correspondence from readers relating to articles published in the Journal. Responses can be sent electronically via the BJS *website (www.bjs.co.uk) or by post. All electronic communications will be reviewed by the Correspondence Editor and a selection will be published in the Journal, together with approved letters submitted by post. Letters must be no more than 250 words in length. Letters submitted by post should be typed on A4-sized paper in double spacing and should be accompanied by a disk*

Sodium hyaluronate enhances colorectal tumour cell metastatic potential *in vitro* and *in vivo* (*Br J Surg* 2001; 88: 246–50)

Sir

We would question the method of tumour load assessment in this paper. The intraperitoneal tumour load was scored by counting the number of tumour nodules but there is no mention about the size of the nodules. We have found that the only way to determine tumour load accurately is by semi-quantitative scoring and taking the varying diameters of the nodules into account[1]. We feel that this is a serious short-coming of the methodology employed by Tan *et al.* making their *in vivo* results questionable.

The authors did not refer to a publication[2] in which we addressed the same concern about the use of sodium hyaluronate, using a similar experimental approach. In that publication we reported the effect of sodium hyaluronate on intraperitoneal growth of a rat colon carcinoma. In contrast to Tan *et al.*, in two different experiments we could not demonstrate a significant effect on tumour growth, defined by an appropriate scoring of tumour load. The final plea that 'this matter deserves careful investigation' has already been carried out.

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Authors' reply

Sir

Instillation of a rat colorectal tumour cell line DHD/K12 into the intraperitoneal cavity of a BD IX rat produces numerous tumour nodules of similar size which are usually less than 1 cm in diameter. The differences in tumour load following different treatments such as taurolidine[1] or sodium hyaluronate (our study) represent the number rather than the size of tumour nodules. The most precise and accurate methods for tumour load assessment are either by directly counting the number of tumour nodules[1] or by weighing the intraperitoneal tumour[2]. The semiquantitative scoring method of Marquet *et al.* in WAG rats using CC-531 tumour cells is not suitable in our experiment. Sodium hyaluronate-induced tumour growth in the intraperitoneal cavity may be tumour cell and model specific. This may explain the negative results obtained by Marquet *et al.*[3]. As the tumour model used by Marquet *et al.* was different we did not refer to it in our study.

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1 McCourt M, Wang JH, Sookhai S, Redmond HP. Taurolidine inhibits tumor cell growth *in vitro* and *in vivo*. *Ann Surg Oncol* 2000; **7**: 685–91.
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Acute-phase protein response, survival and tumour recurrence in patients with colorectal cancer (*Br J Surg* 2001; 88: 255–60)

Letter 1

Sir

The authors argue that 'an acute-phase protein response at 3 months after operation does not have the prognostic significance reported by earlier studies'. In this study, however, C-reactive protein (CRP) was estimated postoperatively in only 88 of 202 patients. The indications for the measurement of CRP in this group of patients are not given. The measurements may have been carried out because of a suspected infection (or inflammation) postoperatively. If this were the case then high values of CRP would obviously not be associated with tumour recurrence. This illustrates the disadvantages of such a retrospective study; although practically difficult, the prognostic value of a variable is best studied in a prospective manner. The other study which showed a correlation between high postoperative CRP levels and tumour recurrence was conducted prospectively[1].

The determination of the significance of the difference in tumour recurrence rates between the two groups with and without an elevated CRP by the χ^2 test is probably not appropriate (as one of the frequencies is less than 5).

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Letter 2

Sir

We read with interest that a bulky colonic carcinoma is more likely than a small tumour to elicit an acute-phase protein response (APPR). We have previously shown that there is a positive correlation between the volume of colorectal liver metastases and the serum level of interleukin 6 that stimulates hepatic production of C-reactive protein (CRP)[1]. However, whether the APPR reflects the tumour's behavioural pattern or an epiphenomenon may be partly addressed by measuring the quality of life indices that are more predictive of survival in patients with colorectal liver metastases than tumour size[2]. The impairment in quality of life is significantly associated with increased serum levels of interleukin 2 soluble receptor α[1] that is a marker for T lymphocyte activation thought to be responsible for inducing an APPR. Furthermore, increased serum levels of CRP and of interleukin 2 soluble receptor α also predict weight loss in patients with metastases that is detrimental to survival[3]. Therefore tumour-related APPR and lymphocytic activation may influence survival by inducing weight loss and quality of life impairment in patients with liver metastases. The latter may be related to the depletion of serum tryptophan by immunological activation that results in an imbalance of the neurotransmitter serotonin[4].

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Authors' reply

Sir

Measurements of C-reactive protein were performed retrospectively on samples collected for carcinoembryonic antigen measurement as part of follow-up and were certainly not taken because of evidence of infection. Furthermore, the concern of Balasubramanian and Dalavaye regarding the validity of using contingency table analysis (χ^2 test) to compare tumour recurrence rates between two groups is misplaced. It is generally accepted that the χ^2 test is valid if at least 80 per cent of the expected frequencies are greater than 5 and all expected frequencies are greater than 1. The magnitude of observed frequencies is largely irrelevant. This rule is clearly satisfied by the analysis under question. The observations by Huang and Tsavellas are interesting and add weight to our hypothesis that there is an association between tumour behaviour, a systemic host response and outcome in patients with colorectal cancer.

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Value and cost of follow-up after adjuvant treatment of patients with Dukes' C colonic cancer (*Br J Surg* 2001; 88: 101–6)

Sir

Patients who underwent salvage surgery in this study had a 5-year survival rate of 40 per cent and a median survival rate of 38 months, compared with a 5-year survival rate of 3 per cent and a median survival rate of 9 months for those unsuitable for salvage surgery. These findings are in contrast to those of a meta-analysis by Bruinvels *et al.*[1] who assessed seven randomized controlled studies. These authors found more asymptomatic recurrences, metachronous tumours, salvage operations and curative resections, with no improvement in overall or cancer-specific survival.

Similarly, four randomized controlled trials examining the same problem have failed to demonstrate any increase in overall survival, despite detecting more recurrences and thereby offering more salvage resections (references 5, 21 and 27 in the study being discussed). This is relevant considering that the present study included only Dukes' C lesions, compared to all stages of colorectal cancer in the other trials; one would have expected a better outcome in Dukes' C disease. Perhaps the dramatic improvement in survival in these patients is due to an alteration in metastatic potential of tumours following chemotherapy? One also wonders whether stage migration is a factor? It should not be forgotten that routine follow-up and reassurance provides psychological support to patients and allows the surgeon an opportunity for audit. The role of general practitioners is relevant in this regard.

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Authors' reply

Sir

We are not aware of evidence that adjuvant chemotherapy has a beneficial effect on tumour behaviour after relapse. These data are available for analysis in trials with an untreated control group. Stage migration might be important in earlier series not using sensitive liver visualization. Our series of patients with Dukes' C colon tumours will have harboured fewer patients with cryptometastatic disease. On the other hand, incorporating significant numbers of patients with early colon cancer in the meta-analysis should have improved the chance of survival after salvage surgery in those studies. Two factors may be crucial in explaining the differences in the results: long-term survival is observed in our patients undergoing liver or colon surgery. The chance for cure from secondary surgery in the rectum is very small and studies of patients with rectal cancer will show worse survival from salvage surgery. The quality of surgery has improved compared to the time of the meta-analysis and the rate of rectal relapse and failed liver surgery will be higher in those studies. The question of optimal follow-up after colon cancer surgery is complex. The balance between reassurance for 'good news', the agony of false positives and the uncertainty after true relapse is not easy to find.

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Randomized clinical trial of diathermy *versus* scalpel incision in elective midline laparotomy (*Br J Surg* 2001; 88: 41–4)

Sir

The authors concluded that there is a significant advantage from the exclusive use of electrocautery in creating a midline abdominal incision, expressed in terms of incision time, blood loss and pain score. They found no significant difference in wound or peroperative complication rates. However, the significant reduction in incision time was based on an analysis that depended on wound area, a factor that would have been equivalent in both groups given adequate sample size and randomization. No significant difference in time to enter the abdomen was found between groups, both being around 8 min. With regard to pain relief we were interested to note the absence of epidural analgesia. The authors point out that the most important issue when using diathermy incision is wound complications. Unfortunately, the sample size of the study was too small to examine this issue adequately. The power is such that it would only identify a minimum infection rate of 27 per cent *versus* their departmental rate of 5 per cent, given a power of 80 per cent and significance level of 0·05. Alternatively, to detect a minimum infection rate of 10 per cent (twice normal) they would have needed 435 patients in each arm. The only valid conclusion to be drawn from this study is that there is a small amount of decreased blood loss from the wound when using diathermy incision. This may be grossly outweighed by a complication rate as yet unknown.

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Author's reply

Sir

It is exactly for the reason raised in this letter that we chose to report opening times per square centimetre and not per wound as this enabled exclusion of wound area as a confounding factor. In our hospital and other units in Ireland there is no epidural service available on the wards. We feel the benefits to the patients of reduced pain and reduced opiate requirements are a significant advantage of diathermy incision. Since this study the senior author has used diathermy exclusively to make abdominal incisions. We feel that this technique is safe and provides a rapid, haemostatic incision that is less painful for the patient.

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Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei (*Br J Surg* 2001; 88: 458–63)

Sir

While congratulating the authors and completely agreeing with the indications for such an aggressive approach I wonder if adjuvant chemotherapy in these patients is really necessary. Since more than 70 treated patients did not benefit from systemic chemotherapy given prior to surgery, why should they benefit after cytoreductive surgery? Endoluminal recurrences at the resection sites are not a major problem and hyperthermic intraperitoneal chemotherapy often results in small and large bowel oedema. What is the rationale for bowel anastomoses after intraperitoneal chemotherapy? Could the rate of enteral fistula be due, at least in part, to the operative techniques? Despite these concerns, the data clearly emphasize that patients with pseudomyxoma peritonei need adequate treatment in specialized centres to avoid inappropriate laparotomy by surgeons less experienced in the treatment of this disease.

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Authors' reply

Sir

Dr Jahne is correct when he emphasizes the lack of reliable data on the effects of 5-fluorouracil-based systemic chemotherapy in the treatment of pseudomyxoma peritonei. The effects in colon cancer are well established. It is sometimes difficult to distinguish clearly between pseudomyxoma peritonei and well differentiated mucinous adenocarcinoma. We therefore add 5-fluorouracil/Leucovorin to our treatment schedule if our pathologists find malignant foci in the resection specimen. We frequently observe pseudomyxoma peritonei recurrence in bowel suture lines of previous operations. We therefore take the precaution to delay suture lines until after the perfusion. Whether this prevents suture line recurrence is difficult to prove. We are currently studying this question in an animal model. Our rate of suture line breakdown was low and seems not to have been influenced by the sequence chosen. Our main problem remains leakage from pinpoint holes in small bowel due to serosal damage after cytoreduction and adhesiolysis especially in reoperative surgery.

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Need for secondary interventions after endovascular repair of abdominal aortic aneurysms. Intermediate-term follow-up results of a European collaborative registry (EUROSTAR) (*Br J Surg* 2000; 87: 1666–73)

Sir

Reporting from a database of 2176 patients, the authors focus on a group of 1023 who survived 12 months after endovascular graft insertion. They exclude all complications within the first month of the original procedure. Thereafter, only the 'most extensive' of multiple interventions are included. Their analysis is not therefore made 'on the intention-to-treat principle' as claimed. Their mean follow-up is only 20 months. How can they justify a results sections on late deaths in this report? The size of aneurysms treated also merits comment. What is the justification for treating patients with aneurysms with diameters of 28–55 mm?

With a 10 per cent reintervention rate, even in this idealized study group, they demonstrate that the current generation of endovascular devices are not robust enough for clinical use. Are the EUROSTAR participants going to stop all further attempts at endovascular aneurysm control in patients? Almost 50 per cent of their patients are classified as American Society of Anesthesiologists grades I and II and should now be offered open aneurysm surgery. Would the authors agree that, at best, the current use of endovascular devices should be confined to developmental research?

Finally, the term endovascular aneurysm repair, although in common usage, is unfortunate. Endovascular interventions never restore vascular integrity to an extent that allows patients to forget about their former life-threatening condition. Endovascular aneurysm control can never be guaranteed for life, as unacceptable reintervention and rupture risks always remain. Perhaps endovascular aneurysm control should be adopted for future use.

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Authors' reply

Sir

Patients' results were included prospectively (for 73 per cent of the patients, as reported), which is after preoperative notification of the planned treatment to the Data Registry Centre. We do not see that selecting the most extensive of redo procedures as an endpoint compromises the intention-to-treat principle and such patients were included in the registry. The mean annual death rate after aneurysm repair was approximately 4 per cent in the reported series, which is in agreement with other reported series. After 3 years the cohort in follow-up still included 286 patients (standard error smaller than 10 per cent), which is a sufficiently large group for a meaningful analysis of the death rate and causes of death within this period.

It was the purpose of the present report to emphasize the relatively frequent need for late revision. We agree that the first and second generation of devices, which constituted the major part of this series, were susceptible to material fatigue and disconnection of different device components. Details of device failure were described extensively in the discussion. It is of note that the majority of revisions were by catheter technique, and only 23 of the 1023 patients required a transabdominal secondary intervention.

Should endovascular technique for aneurysm treatment in general be abandoned because of inferior results? Probably not. Improved device construction, and increased experience of vascular surgeons and interventional radiologists will help overcome the flaws of the technique during the initial years of use. Continued patient and device surveillance after endovascular abdominal aortic aneurysm repair (or control) remains mandatory. Registries, such as EUROSTAR, appear to be useful in identifying adverse events of novel treatment.

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Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis (*Br J Surg* 2000; 87: 1650–5)

Sir

The authors should be commended for their contribution to the rather complex management issues in patients with idiopathic pancreatitis. The article further highlights the limitation of ultrasonographic examination of the gallbladder; 11 of 44 patients had gallbladder stones which were missed on more than one examination. It also draws attention to the issue of biliary sludge/microlithiasis. A previous study[1] concluded that intervention (cholecystectomy/endoscopic retrograde cholangiopancreatography (ERCP)) significantly reduces the incidence of recurrent attacks of pancreatitis. The results of this study fail to show this. Of the 11 patients with microlithiasis, even the five in whom no intervention was carried out did not experience any further attacks of pancreatitis. It would be helpful to know if the authors have more information of further follow-up on this group.

Questions regarding the need for intervention and the most appropriate one in the presence of microlithiasis remain to be answered. In the presence of microlithiasis, do the authors recommend intervention only if the pancreatitis recurs, or even after the primary attack? It is evident that since the advent of laparoscopic cholecystectomy the numbers of cholecystectomies performed have increased[2,3]. There is still not enough evidence that this group of patients benefit from surgery as there are still a few patients who experience further attacks of pancreatitis even after cholecystectomy. These patients probably belong to a group in whom the microlithiasis is related to stasis secondary to sphincter of Oddi dysfunction. On the other hand, ERCP as the sole therapeutic modality does not seem to be justified as biliary sludge on follow-up scans has been shown to develop into gallbladder stones[4].

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1 Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. *N Engl J Med* 1992; **326:** 589–93.
2 Steinle EW, VanderMolen RL, Silbergleit A, Cohen MM. Impact of laparoscopic cholecystectomy on indications or surgical treatment of gallstones. *Surg Endosc* 1997; **11:** 933–5
3 Lam CM, Murray FF, Cuschieri A. Increased cholecystectomy rate after the introduction of laparoscopic cholecystectomy in Scotland. *Gut* 1996; **38:** 282–4.
4 Ros E, Navarros S, Bru C, Garcia-Puges A, Valderrama R. Occult microlithiasis in 'idiopathic' acute pancreatitis: prevention of relapses by cholecystectomy or ursodeoxycholic acid therapy. *Gastroenterology* 1991; **101:** 1701–9.

Authors' reply

Sir

As stated in the original article, one patient with untreated microlithiasis suffered a second attack of pancreatitis 8 weeks after the first. We feel clear evidence of microlithiasis (after feeding has been restarted to reduce biliary stasis) should prompt definitive treatment within 4 weeks of the initial attack as per British Society of Gastroenterology recommendations for gallstone pancreatitis[1]. We disagree that endoscopic retrograde cholangiopancreatography (ERCP) (presumably with sphincterotomy) does not seem justified as the sole treatment modality. In elderly patients in whom the risk of developing symptomatic gallstones is low, it may suffice. In younger patients in whom there is concern regarding long-term sequelae of sphincterotomy and in whom gallbladder stones may develop in the future, laparoscopic cholecystectomy is our preferred treatment.

We believe the hypothesis that recurrent pancreatitis after cholecystectomy is due to sphincter of Oddi dysfunction should be tested only in patients in whom a clear bile duct at the time of surgery has been proven by on-table cholangiography and not preoperative ERCP. It should be remembered that tiny stones may be missed by cholangiography and this remains a difficult problem to solve.

Follow-up of 20 patients revealed a significant reduction in frequency of attacks of acute pancreatitis among those treated for pathology found using endoscopic ultrasonography compared to those in whom no treatment was warranted. The overall morbidity of this approach was only 0·5 per cent. As such, we believe endoscopic ultrasonography is a valuable investigation in idiopathic pancreatitis.

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1 United Kingdom guidelines for the management of acute pancreatitis. British Society of Gastroenterology. Gut 1998; 42 (Suppl 2): S1–13.

Randomized clinical trial of laparoscopic *versus* open appendicectomy (*Br J Surg* 2001; 88: 200–5)

Letter 1

Sir

The authors must be congratulated for successfully recruiting 828 patients in just 19 months. From this study, and others quoted in it, minimal access appendicectomy appears to carry a lower incidence of wound infection and would, logically, be preferable in obese patients presenting with diagnostic uncertainty. Indeed, several authors[1–3] have reported a direct correlation between obesity and increased risk of wound infection. However, it was disappointing to read that the wound complications presented in this study were not correlated with body mass index. In terms of cosmesis, it is hardly surprising that patients preferred the minimal access procedure. It is unfortunate, however, that no data were presented in relation to the actual length of the horizontal incision in the 'open' group. While an apparently normal appendix was removed at open operation, it was left *in situ* in the laparoscopic group. The rationale for this practice seems rather unclear. Regarding the patient who developed a caecal leak, was the base of the appendix gangrenous leading to the sloughing of a ligature? How was this patient subsequently managed?

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1 Pagni S, Salloum EJ, Tobin GR, VanHimbergen DJ, Spence PA. Serious wound infections after minimally invasive coronary bypass procedures. *Ann Thorac Surg* 1998; **66**: 92–4.
2 Israelsson LA, Jonsson T. Overweight and healing of midline incisions: the importance of suture technique. *Eur J Surg* 1997; **163**: 175–80.
3 Bertin ML, Crowe J, Gordon SM. Determinants of surgical site infection after breast surgery. *Am J Infect Control* 1998; **26**: 61–5.

Letter 2

Sir

We were intrigued by this trial showing significantly more intraperitoneal abscesses in patients randomized to laparoscopy (4·6 *versus* 1·0 per cent). They believed the most important reason was the chance inclusion of a greater proportion of patients with more severely inflamed appendices in the laparoscopic group. A simple calculation showed that the difference was merely between 46 and 33 per cent. A subgroup analysis focusing only on patients with gangrenous/perforated appendicitis revealed a threefold increase in the incidence of intraperitoneal abscess in the laparoscopic group (3·0 *versus* 9·2 per cent). Surgical technique was therefore a more important factor than uneven randomization.

The authors alluded to, among other technical points, the possibility of irrigation spreading infected material. We have previously highlighted the risk of energetic irrigation which may disseminate infection to hernial sacs, resulting in scrotal abscess or infected hydrocele[1,2]. We have now abandoned irrigation and, after thorough suction, the peritoneal cavity is meticulously mopped (as in open appendicectomy) with 4 × 4 cm gauze swabs introduced through a 5/10-mm reducing sheath. The added advantage includes confinement of the infected site by several gauze packs during dissection and suction on a gauze obviates blockage of the sucker. Our updated audit showing four intraperitoneal abscesses in 432 laparoscopic appendicectomies (1·1 per cent) compared favourably with that of open appendicectomy[3].

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1 Ng WT, Lau HW. Left scrotal abscess complicating laparoscopic appendicectomy. *Aust N Z J Surg* 1998; **68**: 152–3.
2 Ng WT, Cheng PW. Remedying an intriguing complication of laparoscopic appendicectomy. *Surg Laparosc Endosc* 1998; **8**: 405–6.
3 Lee YK, Sze YS, Yeung HC, Ng WT. Laparoscopic appendicectomy in a community hospital. *Clinical meeting of the Hong Kong Society of Minimal Access Surgery, Panyu, China*, 2 December 2000.

Authors' reply

Sir

In response to the letter from Banerjee, although clinically significant, infectious complications and cosmesis were classified as secondary endpoints in our study. In the absence of prior calculations of sample size and power of secondary endpoints, statistical tests on secondary endpoints must be exploratory, serving to explain or support findings and to suggest further hypotheses for subsequent research. Inclusion of predictor variables such as body mass index and length of incision seems to be most appropriate in studies in which wound infection and cosmesis, respectively, are primary endpoints. There is accumulating evidence, including a pilot study in the *Danish Medical Journal*[1], that a non-inflamed appendix can be safely left *in situ* at laparoscopy, even if another diagnosis is not achieved. The decision to remove a normal looking appendix at open surgery was approved by the ethical committee and primarily based on the possible confusion caused by a transverse scar in the right fossa if the appendix was not removed. The patient with a caecal leak had the first proximal endoloop placed on the elongated caecal wall resulting in necrosis. Following open suture repair and antibiotics the patient recovered uneventfully.

Ng *et al.* are to be congratulated on an intraperitoneal abscess rate of 1·1 per cent. We do agree that surgical factors such as experience or technique influence the rate of developing intraperitoneal abscess in the postoperative period. Until results from controlled trials comparing surgical techniques are available the significance of surgical technique as a risk factor remains speculative. Our study allowed us to identify only the significantly greater proportion of more severely inflamed appendices in patients randomized to laparoscopy as the most probable reason, supporting the findings of others.

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1 Pedersen AG, Petersen OB, Wara P, Qvist N, Laurberg S Laparoscopy in suspected acute appendicitis. Experience with the first 233 laparoscopies at a university hospital department. *Ugeskr Laeg* 1996; **158:** 2377–80

Role of surgery in mild primary hyperparathyroidism in the elderly, Letter 2 (*Br J Surg* 2001; 88: 595)

Sir

We are familiar with Dr Silverberg's study[1] and wish to record that it was not a randomized trial. Patients were simply advised whether or not to undergo surgery on the basis of the guidelines adopted by the National Institutes of Health Consensus Conference[2]. The value of the study was further impaired because 35 of the 121 patients studied opted for a different treatment to that indicated by the protocol. We therefore stand by our observation that no prospective randomized controlled trial comparing parathyroidectomy with conservative management for patients with mild or asymptomatic disease has been published.

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1 Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery *N Engl J Med* 1999; **341:** 1249–55.

2 NIH Conference. Diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement *Ann Intern Med* 1991; **114:** 493–7.

Evaluation of the necessity for gastrectomy with lymph node dissection for patients with submucosal invasive gastric cancer (*Br J Surg* 2001; 88: 444–9)

Sir

This article describes the association of a number of parameters with the presence of lymph node metastasis in patients over a period of almost 20 years. We are not told how the presence or absence of lymph nodal metastasis was determined. Was it recorded from the records or were the sections studied again? This is important because of the possible variation in the method and intensity of the search for lymph node metastases over this time period. It would be important to look for micrometastases in patients with negative nodes before negating the benefits of lymphadenectomy, especially as these patients would not receive adjuvant treatment.

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Authors' reply

Sir

The existence of nodal metastases is based on the pathology report of each patient and not re-evaluation using a new technique such as immunohistochemical staining by cytokeratin antibody. Assessment involved a single section of each node in its longest axis and stained with haematoxylin and eosin. The existence of micrometastases certainly may be a source of residual disease. The incidence of micrometastases in submucosal invasive cancer is reported as 14–23 per cent[1,2]. The reported risk factors for micrometastases are exactly the same as ours and the low-risk group have a limited risk.

We accept that the presence of micrometastases may afford a small, but as yet undetermined, additional risk and agree that careful follow-up of locally resected patients is mandatory. Such risks should be explained to patients when informed consent is obtained.

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1 Ishida K, Katsuyama T, Sugiyama A, Kawasaki S. Immunohistochemical evaluation of lymph node micrometastases from gastric carcinomas. *Cancer* 1997; **79:** 1069–76.
2 Kashimura H, Ajioka Y, Watanabe H, Nishikura K, Iiri T, Asakura H. Risk factors for nodal micrometastasis of submucosal gastric carcinoma: assessment of indications for endoscopic treatment. *Gastric Cancer* 1999; **2:** 33–9.

Randomized clinical trial of *Helicobacter pylori* from dental plaque (*Br J Surg* 2001; 88: 206)

Sir

Butt *et al.* base their study on a conclusion from the work of Desai *et al.*[1] which suggests that *Helicobacter pylori* in dental plaque is more resistant to conventional therapy as used for gastric organisms. Having shown how the oral population of *H. pylori* may be controlled, do the authors propose to study patients endoscoped both before and after gastric and dental treatment? This might be in the form of a randomized controlled trial, with groups assigned to those receiving or not receiving oral treatment in addition to triple therapy.

The assumption the authors made is reasonable, but does not consider environmental factors such as person-to-person transmission, as suggested by Berkowicz and Lee[2], or *H. pylori* in patients without dental plaque who may be acquiring it by other means than from the environment. The evidence perhaps needs to be stronger if the recommendation is to send patients with antral *H. pylori* gastritis for dental assessments.

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1 Desai HG, Gill HH, Shankaran K, Mehta PR, Prabhu SR. Dental plaque: a permanent reservoir of *Helicobacter pylori*? *Scand J Gastroenterol* 1991; **26:** 1205–8.
2 Berkowicz J, Lee A. Person-to-person transmission of *Campylobacter pylori*. *Lancet* 1987; **2:** 680–1.

Author's reply

Sir

The relevance of *H. pylori* in the oral cavity is still unknown. The pilot study raised several interesting questions, namely the potential source of the dental plaque for gastric re-infection following triple therapy. The proposed study by Mr Chaudhuri is of interest but our first priority is to improve the laboratory identification of the micro flora. We recognize the need to undertake a more sophisticated identification of *H. pylori*.

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Surgical Endocrinology

G. M. Doherty and B. Skogsheid (eds)

285 × 218 mm. Pp. 618. Illustrated. 2000. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins. $175·00.

This is a multiauthor (72 contributors), major textbook. The contributors comprise many of the academics in the American Association of Endocrine Surgeons, as well as selected members of the International Association of Endocrine Surgeons in Sweden, Italy, Germany and France. Alas, only one of the 41 chapters comes from Britain. The book has the provenance of many experts in the field and has the freshness of being published in first edition. Much is new and is for the first time transposed from journals to a book. The detailed current understanding of the genetics of the multiple endocrine neoplasia (MEN) 1 and MEN 2 syndromes are excellent examples of this. Laparoscopic approaches are well described, particularly that of adrenalectomy. Some chapters are detailed and almost comprehensive; the chapter on the Zollinger–Ellison syndrome is an example, standing as a benchmark of a comprehensive review by a single author. I do not think there is a book quite like it. There are many books on endocrine surgery and surgical endocrinology, but none as extensive as this. It is suitable for libraries, endocrine surgeons, endocrinologists who wish to check surgical indications and techniques, and trainees with an eye to specialization in the field.

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Office Urology: The Clinician's Guide

E. D. Kursh and J. C. Ulchaker (eds)

259 × 181 mm. Pp. 530. Illustrated. 2000. Totowa, New Jersey: The Humana Press. $99·50.

In the preface of this offering the editors claim that they present a fresh, practical and concise textbook, covering vital issues that the urologist must face on a daily basis in the office. This claim is certainly justified and, as a basic text for the general urologist or urological trainee, I found it to be quite superb. Despite it being multiauthored, it is very consistent in style and standard, and I found my approach of reviewing each chapter individually to be somewhat redundant because of this. A major portion of the urologist's activity is 'frontline practice' in an office or outpatient setting. This text will greatly assist the inexperienced urologist or trainee in meeting the challenges presented. While the authorship contains many of the famous names of urology, the presented material benefits greatly from the 'coal-face experience' of the majority of the authors. The European, and particularly British, reader will be a little uncomfortable with the first section on management, marketing, billing and legal issues; while these issues are important and occupy less than 20 per cent of the text, this reader was happy to move on to the next section.

The full range of general urology is covered and, while topics are presented in a didactic manner, the opinions presented are fair and well balanced. It is difficult to single out particular chapters for commendation; however, I especially liked the one on practical dermatology for the urologist (but felt that duplicating photographs in black and white that also appear in colour in the same chapter was unnecessary). In the section on advanced prostate cancer I would have welcomed a little more on the management of hormone-escaped cancer. The chapter on erectile dysfunction was, perhaps, a little short and I was surprised that, despite there being a chapter on common paediatric problems, nocturnal enuresis was dealt with in half a page. Any criticism, however, is more than outweighed by the excellence of this publication. It is comprehensive, authoritative and extremely useful for the general urologist. I certainly intend referring to it and can see a requirement for future editions as changes in office urological practice occur.

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Care of the Critically Ill Surgical Patient

I. D. Anderson (ed)

244 × 187 mm. Pp. 176. Illustrated. 1999. London: Arnold. £32·50.

There is a real need for a practical guide to the care of the critically ill surgical patient. It is important that surgeons accept responsibility for patients under their care but, unless they understand the principles and practice of such care, it is impossible for them to fulfil this responsibility and to have meaningful discussions with other colleagues. This book fills this gap admirably. For the most part it provides a well structured practical guide that is firmly based on good scientific principles. The method of presentation, judicious use of bold type and careful combination of facts, case history, practical skills and summaries makes for easy reading and assimilation.

Any criticism of this publication should not detract from overall appreciation of its quality. However, mention of the CCCrISP course is frequent and somewhat irritating. It is questionable in the critically ill patient whether any investigation should be 'routine' (p. 18). Some explanation of the critical value of a haemoglobin level of 10 g/dl should be included. There are very few grammatical errors but the sentence relating to 'minute volume' and the chapter on respiratory failure do not make sense. In the critically ill patient the clinical assessment of central venous pressure cannot be justified and not all cardiologists would agree that the combined use of beta-blockers and amiodarone is contraindicated. In the chapter on shock, the important surgical condition of acute pancreatitis is not mentioned as a cause of hypovolaemia; discarding the RANSON and IMRIE scores without further discussion seems inappropriate. Some recommendations are difficult to justify, for example the use of diagnostic peritoneal lavage for obscure acute abdomen in sick patients, but overall the information is provided in a balanced and rational way. The importance of communication cannot be overemphasized and so Chapter 11 seems to sit uncomfortably in the sequence of chapters; it would seem more appropriate to have this as Chapter 2 or 3. The chapter on nutrition stands out as being the most disappointing; the use of anthropometric techniques is of no value in the assessment of individual patients. The use of nitrogen balance studies is, at best, of dubious value without improvement in protein status. There is little evidence of benefit of total parenteral nutrition (TPN) in inflammatory disease of the gastrointestinal tract and, indeed, there is clear evidence in the literature that TPN is associated with an increased risk of complications, particularly sepsis, in all but a minority of patients. In contrast, the chapter on pain management is both important and valuable; this subject is poorly understood and applied in clinical practice.

As indicated above, these relatively minor criticisms should not be allowed to detract from the fact that this publication can be recommended to all clinicians involved in the care of surgical patients. It is to be hoped, if the principles are applied, that the number of patients who become critically ill may be reduced drastically.

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Oxford Textbook of Surgery. 2nd Ed.

P. J. Morris and W. C. Wood (eds)

282 × 223 mm Pp. 3701. Illustrated 2000 Oxford: Oxford University Press
£295 00

The preface to the first edition of this textbook stated that the intention was 'to present a picture of surgery in its totality'. These volumes accomplish this monumental task and, to my mind, provide a body of work that is the leader in its field. Experienced surgeons and trainees in both developed and developing countries will find it more than a basic textbook; it is also an invaluable reference across the broad expanse of surgical specialties. Since the first edition a number of changes have been made. William C. Wood of Emory has replaced Ronald Malt as joint editor and the authorship has broadened, being now less directly related to the mother institutions of Harvard and Oxford. Many chapters have been rewritten and updated to acknowledge new developments that have taken place in recent years such as, for example, in minimally invasive surgery. New topics include response to injury, trauma and shock, surgical nutrition, evidence-based approaches and molecular medicine.

The chapters are clearly presented and beautifully illustrated, the text reads smoothly and the topics achieve a satisfactory balance of approaches from both sides of the Atlantic. Although not comprehensive in each discipline, they provide an excellent synopsis of most aspects of surgery and will give practical help in managing surgical patients, particularly those who have problems that lie outside one's own area of expertise. They provide an immediacy of access with which the web is still, as yet, unable to compete. It has been estimated that the sum of medical knowledge doubles every 19 years. Just 6 years have elapsed since the first edition and the pity is that you may not have a chance to read all the beautifully prepared sections in this edition before the next is on the shelves.

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Scientific Surgery

The *BJS* is committed to the practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on the *BJS* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Lau LL, Gardiner KR, Martin L, Halliday MI, Hannon RJ, Lee B *et al.* Extraperitoneal approach reduces neutrophil activation, systemic inflammatory response and organ dysfunction in aortic aneurysm surgery. *Eur J Vasc Endovasc Surg* 2001; **21:** 326–33.

Multiple organ dysfunction scores and systemic inflammatory response scores were significantly lower after extraperitoneal, as compared to transperitoneal, aneurysm repair in this study of 20 patients

Heyland DK, Montalvo M, MacDonald S, Keefe L, Su XY, Drover JW. Total parenteral nutrition in the surgical patient: a meta-analysis. *Can J Surg* 2001; **44:** 102–11.

A total of 27 randomized trials were available for study. The studies were heterogeneous, but nutrition appeared to reduce complication rates after surgery, particularly in malnourished patients, but had no effect on mortality

Scatton O, Meunier B, Cherqui D, Boillot O, Sauvanet A, Boudjema K *et al.* Randomized trial of choledochocholedochostomy with or without a T-tube in orthotopic liver transplantation. *Ann Surg* 2001; **233:** 432–7.

This was a multicentre study of 180 liver transplants. Use of a T tube increased the total number of biliary complications, including cholangitis and fistula (10 *versus* 2·2 per cent) There was no difference in graft or patient survival rates

McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM *et al.* Subcutaneous heparin *versus* low molecular weight heparin as thromboprophylaxis in patients undergoing colorectal surgery. Results of the Canadian colorectal DVT prophylaxis trial: a randomized, double–blind trial. *Ann Surg* 2001; **233:** 438–44.

Some 936 patients were randomized to enoxaparin 40 mg per day or calcium heparin 5000 μm 8 hourly. No patient died from pulmonary embolism, thromboembolic complications and bleeding rates were similar.

Cejna M, Thurnher S, Illiasch H, Horvath W, Waldenberger P, Hornik K *et al.* PTA *versus* Palmaz stent placement in femoropopliteal artery obstructions: a multicentre prospective randomized study. *J Vasc Interv Radiol* 2001; **12:** 23–31.

The study included 154 legs in 141 patients. Initial technical success rate was higher using a stent (99 *versus* 84 per cent, *P* = 0·009), but thereafter, clinical and haemodynamic success rates after 1 and 2 years were similar

Minar E, Pokrajac B, Maca T, Ahmadi R, Fellnar C, Mittlböck M *et al.* Endovascular brachytherapy for prophylaxis of restenosis after femoropopliteal angioplasty: results of a prospective randomized study. *Circulation* 2000; **102:** 2694–9.

Radiation therapy improved the rates of restenosis after 6 months (28 *versus* 54 per cent) and vessel patency at 1 year (63 *versus* 35 per cent) in this trial including 113 patients

Cohn SM, Giannotti G, Ong AW, Varela JE, Shatz DV, McKenney MG *et al.* Prospective randomized trial of two wound management strategies for dirty abdominal wounds. *Ann Surg* 2001; **23:** 409–13.

Fifty-one patients were randomized to primary or delayed closure. The wound infection rate was higher after primary closure, but the overall duration of hospital stay and hospital costs were similar

Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe–Rague S, Durieu I *et al.* Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis of pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001; **103:** 2453–60.

These two trials involved 736 patients with first thrombosis and low risk factors. In patients who had an isolated calf vein thrombosis, there was no advantage of 12 over 6 weeks anticoagulation; in patients with proximal deep vein thrombosis, there was no advantage of 6 over 3 months anticoagulation

Pelz RK, Hendrix CW, Swoboda SM, Diener West M, Merz WG, Hammond J *et al.* Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. *Ann Surg* 2001; **233:** 542–8.

Some 260 patients in an intensive care unit for at least 3 days were enrolled There was no improvement in the mortality rate but fluconazole reduced the risk of fungal infection by 55 per cent

The *BJS* website can be found at *http://www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

Surgical Infection Society of Europe abstracts

The following abstracts were presented to the 14th annual meeting of the Surgical Infection Society of Europe held in Gdansk, Poland on 31 May–2 June 2001

Elucidation of the intracellular pathway by which dopamine induces neutrophil apoptosis and identification of membrane-bound dopamine receptors

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Background: Dopamine induces polymorphonuclear neutrophil (PMN) apoptosis, which may partly explain the beneficial effects of dopamine administration to septic patients. This study investigated whether dopamine receptors (D_{1-5}) are expressed on PMNs and whether dopamine influences mitochondrial membrane depolarization (mΩ), intracellular calcium concentration $[Ca]_i$ and caspase 3 activity, which are all recognized contributors to the regulation of apoptosis.

Methods: Dopamine was prepared in concentrations of 10 and 100 $\mu mol\,l^{-1}$. PMN apoptosis was assessed by means of propidium iodide staining and mean channel fluorescence (MCF) on flow cytometry (FC) at 4-h timepoints. In control and dopamine-treated PMNs, the parameters mΩ, $[Ca]_i$ and activity of caspase 3 were measured with the chromophore JC-1 (FC), the calcium-specific probe fura-2 (FC) and Western immunoblotting respectively. Dopamine receptors were identified using polyclonal antibodies (FC) to receptors D_{1-3} and immunohistochemical analysis for D_{4-5}.

Results: The *Table* gives the results when dopamine was used in a concentration of 100 $\mu mol\,l^{-1}$.

Receptors D_{1-2} and D_5 were identified on human PMNs by flow cytometry and immunohistochemistry. Dopamine induced increased caspase 3 protein expression as measured by Western immunoblotting. The D_1/D_5 agonist fenoldopam and adrenaline directed at putative β-adrenergic receptors were unable to reproduce the pro-apoptotic effects of dopamine.

	Apoptosis (%)	mΩ (MCF)	$[Ca]_i$ (MCF)
Control			
4 h	10(2)	943(42)	83(3)
8 h	22(6)	723(15)	96(5)
12 h	39(8)	678(22)	132(8)
Dopamine			
4 h	14(9)	808(17)*	90(3)*
8 h	34(7)*	450(43)*	100(3)*
12 h	57(6)	378(61)*	162(10)*

Values are mean(s.d.). *$P < 0·05$ *versus* control (analysis of variance)

Conclusion: Dopamine induction of PMN apoptosis is associated with significant increases in mΩ and $[Ca]_i$, which translates into pro-apoptotic activity as evidenced by pronounced caspase 3 expression. These findings shed further light on the inflammatory effects of dopamine on innate immunity.

Increased CD95–CD95L-mediated epithelial apoptosis predisposes to pouchitis in patients following ileal pouch–anal anastomosis

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Background: The aetiology of pouchitis, a condition affecting up to 40 per cent of patients following restorative proctocolectomy (RP), remains unknown. Similarities with ulcerative colitis may reflect an autoimmune aetiology. Resolution with metronidazole points to a microbial aetiology. The role of apoptosis in pouchitis was investigated.

Methods: Two groups of patients were recruited. Patients in group 1 ($n = 12$) had known pouchitis and those in group 2 ($n = 12$) were free from pouchitis. Cell-surface fas ligand (FasL) was detected immunohistochemically. Cytoplasmic caspase activity was detected by means of a monoclonal antibody (M30). Terminal deoxyribonucleotidyl transferase-mediated 2′-deoxyuridine 5′-triphosphate nick end labelling (TUNEL) was used to identify DNA fragmentation and nuclear changes. Villous atrophy (epithelial surface length/lamina propria surface area) was assessed histologically and correlated with apoptosis.

Results: A significant increase in epithelial TUNEL, M30 immunoreactivity and villous atrophy was seen in group 1 patients. Upregulation of FasL was characteristic of this epithelium. Increased epithelial apoptosis correlated with increased villous atrophy.

	Group 1	Group 2
TUNEL	0·091(0·04)†	0·0357
M30*	0·225(0·05)†	0·082(0·03)
Villous atrophy (inverse ratio)	0·035‡	0·10(0·03)

Values are mean(s.d.). *M30 apoptotic indices (apoptotic/non-apoptotic cells). †$P < 0·01$, ‡$P < 0·05$ *versus* group 2 (Wilcoxon rank sum test)

Conclusion: An upregulation of Fas–FasL (CD95–CD95L)-mediated epithelial apoptosis, similar to that occurring in ulcerative colitis, predisposes to pouchitis. Increasing levels of epithelial apoptosis and villous atrophy may predispose to local infection and hence to pouchitis. These findings point to a multifactorial aetiology in pouchitis and highlight a putative interaction between autoimmune and microbial factors.

Vasopressor-induced upregulation of endothelin concentration in portal venous blood correlates with mucosal pH decrease and mucosal damage

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Background: Vasopressive therapy with adrenaline (epinephrine) in septic shock has been shown to induce intestinal acidosis and impairment of splanchnic perfusion. The same effects are caused by infusion of endothelin (ET). ET secretion is upregulated *in vitro* and *in vivo* by adrenaline. The present study investigated the hypothesis that adrenaline-treated porcine endotoxic shock was associated with upregulation of ET production.

Methods: The effects of adrenaline (A) and noradrenaline (NA) on ET concentration in portal venous blood, and messenger RNA (mRNA) expression of ET in the mesenteric lymph nodes, small bowel, liver and spleen of pigs exposed to catecholamine-treated endotoxin (lipopolysaccharide; LPS), were studied for 4 h. Sigmoid colon mucosal pH_i and damage were also investigated. To mimic the situation of intensive care therapy in humans, catecholamine therapy was administered individually to maintain blood pressure at a defined level.

Results: Both catecholamines significantly increased mean (s.e.m.) overall ET concentration in the portal vein compared with that in animals receiving LPS only: LPS + A 13·8(2·3) pg ml^{-1} *versus* LPS 9·1(0·2) pg ml^{-1} ($P<0·04$) and LPS + NE 16·1(1·7) pg ml^{-1} *versus* LPS 9·1(0·2) pg ml^{-1} ($P<0·02$). The increased ET concentration in portal venous blood correlated with a decrease in intestinal mucosal pH_i (correlation −0·59, $P<0·0001$) and mucosal damage (correlation 0·93, $P<0·005$). At 4 h only very low amounts of mRNA expression for ET were detectable in all tissues investigated. In contrast to the changes in portal venous blood, mean(s.e.m.) ET mRNA expression was significantly higher in animals that received LPS, in spleen (41·1(9·6) *versus* 20·6(4·8) units; $P<0·05$), mesenteric lymph nodes (19·0(6·2) *versus* 3·5(0·7) units; $P<0·004$) and small bowel (9·7(2·6) *versus* 3·4(0·6) units; $P<0·02$), compared with values in animals in the LPS + NA group.

Conclusion: Vasopressor therapy of LPS shock upregulates the production of the potent vasoconstrictor ET in portal venous blood. This increase correlates with mucosal pH_i and damage. Organs of the abdominal compartment, however, do not seem to be the source of ET.

Activity of three antibiotic-coated/impregnated central venous catheters against *Klebsiella pneumoniae*

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Background: Antibiotic-coated or -impregnated catheters are resistant to colonization of Gram-positive bacteria on their surfaces. However, their activity against Gram-negative bacteria is unknown. The aim of this study was to evaluate and compare the adherence to and persistence of *Klebsiella pneumoniae* on catheter surfaces and also to assess bacteriostatic and bactericidal levels.

Methods: Catheters were silver sulphadiazine–chlorhexidine impregnated (SSC), polyurethane-based oligon polymer containing silver, platinum and carbon black (OP), and minocycline and rifampicin bonded (MR). A non-antiseptic catheter was used as the control group. Catheter segments of 1 cm were immersed in 1 ml phosphate-buffered saline 0·01 mol l^{-1} with 0·25 per cent dextrose (PBSD) and incubated at 37°C. The PBSD was replaced daily. Effluents were frozen at −70°C for subsequent determination of bacteriostatic and bactericidal activity. On days 1, 3, 7, 14 and 21 after initial immersion, 1 ml standardized inoculum of *K. pneumoniae* was added to 90 tubes for a period of 30 min. The inoculum was then replaced with PBSD. One-third of the samples were sonicated immediately (20 kHz, 60 s) and plated for the determination of bacterial adherence. The remaining segments were incubated for 4 and 24 h, followed by the same procedure to determine bacterial persistence with time. All plates were read after 24 h of incubation.

Results: There was a significant reduction in bacterial adherence and persistence for SSC and OP catheters compared with the control group on all days ($P<0·001$). The MR catheter showed significant reduction in adherence on days 1 and 3 only ($P<0·05$). Effluent studies indicated that the impregnated agents in the SSC catheter were bactericidal compared with those in the MR catheter, which were bacteriostatic to *K. pneumoniae*. The activity from the effluents of the SSC and MR catheters disappeared by day 7. No antibacterial activity was detected in the effluents from the OP catheter.

Conclusion: SSC and OP catheters are effective in eliminating *K. pneumoniae* from their surfaces for at least 21 days. Antimicrobial action is eluted from SSC and RF catheters, but not from OP catheters.

Oral glutamine improves the mucosal barrier in radiation enteritis

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Background: The pathogenesis of radiation enteritis can be explained by oxidative stress injury. Glutamine has antioxidant and atrophic effects on the intestinal mucosa.

Methods: The study was conducted in five groups, each of ten rats: group 1, control animals; group 2, radiotherapy; group 3, oral glutamine (before radiotherapy); group 4, oral glutamine (after radiotherapy); group 5, oral glutamine (before and after radiotherapy). Radiotherapy was administered as a single 1000-cGy dose to the abdomen of experimental animals. All rats were killed on day 8 and a midline laparotomy was performed under sterile conditions. Some 2 cm of jejunal segment was excised for histopathological examination and mesenteric lymph nodes (MLNs) were removed for determination of bacterial translocation.

Results: Villous counts were much greater in controls and group 5 animals than in the other groups. Villous height was greater in groups 4 and 5 than in the others. Mitotic activity was also greater in group 5 than in the other groups ($P < 0{\cdot}05$, Mann–Whitney *U* test). Culture-positive MLNs were found in 10, 70, 40, 20 and 30 per cent of groups 1, 2, 3, 4 and 5 respectively.

Conclusion: Oral glutamine administration before and after radiotherapy has a beneficial effect on the intestinal mucosa in radiation enteritis in this animal model.

Inhibition of inflammatory signal transduction in bacterial lipoprotein-tolerized human monocytes

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Background: Both endotoxin (lipopolysaccharide; LPS) tolerance and bacterial lipoprotein (BLP) tolerance represent an essential control mechanism during sepsis. It has been demonstrated previously that BLP tolerance is superior to LPS tolerance in protecting against septic shock-induced death, but the underlying mechanism involved in BLP tolerance is not clear. This study investigated the alterations in inflammatory signal transduction pathways following BLP tolerance.

Methods: BLP tolerance and LPS tolerance in human THP-1 monocytic cells were induced in either serum-present or serum-free culture systems to evaluate the involvement of soluble CD14. Tolerized cells were further stimulated with high doses of BLP or LPS. Tumour necrosis factor (TNF) α and interleukin (IL) 6 levels were determined by enzyme-linked immunosorbent assay. Toll-like receptor (TLR) 2 and mitogen-activated protein kinases (MAPKs), including extracellular signal regulated kinase (ERK), Jun N-terminal kinase (JNK) and p38 kinase, were detected by Western blotting. Nuclear factor (NF) κB activation was assessed by transfection of the pNF-κB–luciferase reporter vector and electrophoretic mobility shift assay (EMSA). A number of MAPK and NF-κB inhibitors were also used to determine which signal pathway was involved in BLP tolerance.

Results: BLP-tolerized monocytes showed a significantly reduced TNF-α production in response to high doses of BLP (41(9) *versus* 2341(537) pg ml^{-1} in non-tolerized cells; $P < 0{\cdot}01$) or LPS (30(8) *versus* 1001(147) pg ml^{-1} in non-tolerized cells; $P < 0{\cdot}01$). Use of specific CD14-blocking monoclonal antibodies and a serum-free culture system revealed that induction of BLP tolerance was independent of both membrane and soluble CD14. BLP tolerance as well as LPS tolerance inhibited phosphorylation of ERK, JNK and p38 kinase, and activation of NF-κB in response to subsequent BLP or LPS stimulation. There was a marked downregulation of TLR-2 expression in BLP-tolerized cells, whereas LPS tolerance did not affect TLR-2 expression.

Conclusion: These results indicate that LPS and BLP tolerance share similar intracellular mechanisms. The critical difference between each peptide relates to differential expression of TLR-2 and TLR-4.

Combination therapy with interleukin 2 and granulocyte–macrophage colony-stimulating factor is protective against peritonitis without lung damage

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Background: Interleukin (IL) 2 and granulocyte–macrophage colony-stimulating factor (GM-CSF) are effective in decreasing the mortality rate in rats with sepsis. This study examined the effects of combining the two agents on local and systemic inflammatory responses.

Methods: Sprague–Dawley rats underwent caecal ligation and puncture (CLP). Mortality was studied in four groups: group 1, CLP alone; group 2, CLP and antibiotics (clindamycin and tobramycin); group 3, CLP, antibiotics and IL-2 ($3{\cdot}0 \times 10^6$ units kg^{-1} intraperitoneally, 120 min before CLP); group 4, CLP, antibiotics, IL-2 and GM-CSF (1 ng g^{-1} daily subcutaneously, after CLP). Myeloperoxidase (MPO) concentration was measured 5 and 18 h after operation in both the peritoneal cavity and lung tissue.

Results: The mortality rate in group 3 was ten of 30, lower than that in groups 1 and 2 (21 and 24 of 30 respectively; $P < 0{\cdot}05$). In group 4 the mortality rate was reduced to one of 30. An increased mean(s.d.) peritoneal MPO concentration at 5 and 18 h was noted in group 3 (17·0(3·8) and 15·5(7·4) units min^{-1} ml^{-1}) and group 4 (13·7(4·2) and 12·6(12·1) units min^{-1} ml^{-1}) in comparison with group 2 (2·4(1·8) and 4·9(3·5) units min^{-1} ml^{-1}; $P < 0{\cdot}05$). No significant increase in MPO levels with respect to group 2 (11·3(2·9) units min^{-1} g^{-1})

was found in group 3 (10·9(2·5) and 11·4(3·0) units min^{-1} g^{-1}) or group 4 (10·6(2·6) and 15·5(3·0) units min^{-1} g^{-1}) at 5 and 18 h respectively.

Discussion: Combination of IL-2 with GM-CSF provides greater protection against sepsis than IL-2 alone. Low mortality after cytokine therapy is not associated with systemic inflammatory involvement (pulmonary MPO), but inflammation is stimulated locally.

Tumour necrosis factor *Nco*I polymorphism as a predictor of postoperative complications

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Background: In severe sepsis and trauma, *Nco*I polymorphism within the tumour necrosis factor (TNF) gene has been shown to be associated with a poor outcome in patients homozygous for *TNFB2/B2*. However, it is unknown whether *Nco*I polymorphism may be a predictor for severe postoperative complications in general surgery.

Methods: To test this hypothesis 127 patients undergoing oesophagectomy, gastrectomy, liver resection, Whipple procedure and (low) anterior colonic resection were included in a prospective study. A fragment of genomic DNA including the polymorphic site of the restriction enzyme *Nco*I was amplified by means of the polymerase chain reaction. The genotype of each patient was determined after *Nco*I digestion of the amplified product. In each patient, perioperative risk was assessed by means of the Physiological and Operative Severity Score for the enUmeration of Mortality and morbiditiy (POSSUM) and postoperative complications were evaluated during hospital stay by a team not involved in patient care. Pneumonia, intra-abdominal abscess, anastomotic leakage and sepsis were regarded as severe postoperative complications.

Results: Genotype distribution was comparable with that of healthy controls, with 9 per cent of the patients homozygous for *TNFB1*, 39 per cent heterozygous for *TNFB1/B2* and 52 per cent homozygous for *TNFB2*. Demographic data were not different between the genotypes. Predictive and actual overall morbidity rates of 70 per cent were comparable between the different groups. The mortality rate was 2 per cent in patients who were heterozygous and 6 per cent in those who were homozygous for *TNFB2*, while there was no death in patients homozygous for *TNFB1*. The rate of severe complications was between 31 and 34 per cent, and showed no difference between the three genotype groups.

Conclusion: A genetic background for severe postoperative complications cannot be demonstrated with *Nco*I polymorphism as a marker within the TNF gene.

Bacterial lipoprotein and lipopolysaccharide tolerance in macrophages is mediated by interleukin 1 receptor-associated kinase phosphorylation

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Background: Interleukin 1 receptor-associated kinase (IRAK), an intracellular signal transducer for pro-inflammatory cytokines, has been thought to participate in the Toll-like receptor (TLR)-mediated innate immune response to lipopolysaccharide (LPS). It has previously been shown that bacterial lipoprotein (BLP) tolerance can protect against BLP- and LPS-induced lethality. To elucidate further the signal transduction pathway for BLP and LPS tolerance, IRAK activation in BLP- and LPS-tolerized macrophages was assessed and the effect of tyrosine kinase inhibition on LPS-, BLP- and LPS + BLP-induced tumour necrosis factor (TNF) α production in macrophages was studied.

Methods: RAW 264.7 macrophages were pretreated or tolerized with medium, LPS or BLP (10 ng ml^{-1}) for 24 h. Cells were then stimulated with LPS, BLP and LPS + BLP (100 and 1000 ng ml^{-1}). Activated intracellular IRAK was determined by Western immunoblotting. In a separate experiment, RAW macrophages were pretreated with control medium, AG126 or AG556 (10, 50, 100 mmol l^{-1}) for 1 h. Cells were stimulated with LPS, BLP and LPS + BLP at doses of 100 and 1000 ng ml^{-1}. TNF-α levels were measured by immunosorbent assay.

Results:

	TNF-α production (ng ml^{-1})		
	Medium	AG126	AG556
100 ng ml^{-1}			
LPS	20(0·8)	3·0(0·4)*	1·7(0·3)*
BLP	28(0·9)	2·7(0·3)*	4·9(0·7)*
LPS-BLP	30(0·6)	2·3(0·2)*	5·7(0·5)*
1000 ng ml^{-1}			
LPS	22(2·8)	2·7(0·04)*	2·3(0·06)*
BLP	24(0·8)	2·6(0·3)*	3·5(0·1)*
LPS-BLP	28(1·3)	2·2(0·2)*	3·6(0·5)*

Values are mean(s.d.) *$P < 0·001$ *versus* control (analysis of variance)

Tyrphostin pretreatment produced a dose-dependent decrease in TNF-α production. This attenuation was seen in all groups, which suggests that the signal transduction pathway via TLR-2 and TLR-4 is mediated by IRAK. Western blot analysis demonstrated upregulation of IRAK in macrophages stimulated with LPS, BLP and LPS + BLP. However, there was a marked downregulation of activated IRAK protein in both BLP- and LPS-tolerant macrophages, the effect being more dramatic in BLP-tolerant cells.

Conclusion: IRAK serves as a common upstream signal transducer of proinflammatory cytokine production for BLP and LPS. Inhibition of IRAK activation is intrinsic to BLP and LPS tolerance-induced changes in TLR-dependent proinflammatory pathways.

Antiseptic agents decrease the production of tissue-type plasminogen activator and plasminogen activator inhibitor type 1 in a human *in vitro* model of peritonitis

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Background: Fibrin deposition is a crucial mechanism of the peritoneal response to intra-abdominal infection. The influence of taurolidine (TAU) and polyhexanid (HEX) on the production of tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor (PAI) type 1 was investigated.
Methods: Human umbilical vein endothelial cells (HUVECs) and human peritoneal mesothelial cells (HPMCs) were grown on collagen-coated filter inserts (HUVECs on the bottom, HPMCs on the top) in a two-chamber culture. After confluence was reached, HPMCs were stimulated with 0·5 ml tumour necrosis factor (TNF) α 10 μg ml^{-1} for 4 h. Afterwards 0·5 ml TAU (1 and 2 per cent) or 0·5 ml HEX (0·1 and 0·2 per cent) solution was added to the upper compartment. After 3 and 7 h aliquots were taken from both compartments and tPA and PAI-1 concentrations were measured by enzyme-linked immunosorbent assay. Controls were either TNF-α-stimulated HPMCs or stimulated HPMCs in culture medium.
Results: Stimulation with TNF-α led to a significant time-dependent increase in tPA and PAI-1 secretion, predominantly to the apical (peritoneal) compartment ($P < 0.05$). After substitution of the stimulus by culture medium, tPA and PAI-1 levels in the apical compartment were almost comparable to TNF controls. Addition of TAU and HEX in both concentrations resulted in initially (3 h) comparable, and after 7 h significantly lower, tPA levels compared with TNF controls ($P < 0.05$). During the observation period TAU led to no further changes. TAU and HEX also led to significantly lower PAI-1 levels in comparison with TNF controls.
Conclusion: Both antiseptic solutions reduced tPA and PAI-1 expression irrespective of continuous stimulation in this model. The decrease in tPA and PAI-1 levels by TAU as well as HEX seems to reflect cellular damage.

Effect of surfactant phospholipids on the production of cytokines by human pulmonary macrophages

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Background: Changes in the amount and composition of pulmonary surfactant are important features of the adult respiratory distress syndrome (ARDS). Because activated lung macrophages may be exposed to surfactant during ARDS, it was hypothesized that surfactant might modulate their activity. It has previously been shown that surfactant protein A (SP-A) inhibits the lipopolysaccharide (LPS)-induced tumour necrosis factor (TNF) α response of both interstitial and alveolar human macrophages. The aim of the present study was to investigate the effect of individual phospholipids contained in surfactant on the production of cytokines and other inflammatory mediators by two well defined subpopulations of human pulmonary macrophages.
Methods: Surfactant and both alveolar and interstitial macrophages were obtained from multiple organ donor lungs by bronchoalveolar lavage and enzymatic digestion. SP-A was purified from isolated surfactant using sequential butanol and octyl glucoside extractions. After 24 h of preculture, purified macrophages were cultured for 24 h in the presence or absence of LPS 10 μg ml^{-1}, phosphatidylcholine (PC) 0·5 mmol l^{-1}, dipalmitoyl phosphatidylcholine (DPPC) 0·5 mmol l^{-1}, SP-A 50 μg ml^{-1}, and combinations. Nitric oxide and carbon monoxide generation (pmol per μg protein), cell guanosine 3′,5′-cyclic monophosphate (cGMP) content (pmol per μg protein), and TNF-α, interleukin (IL) 1 and IL-6 release into the medium were determined.
Results: LPS-induced TNF-α, IL-1 and IL-6 release was not affected by surfactant phospholipids in alveolar or interstitial macrophages, nor did they modify the inhibitory effect of SP-A on cytokine secretion. In interstitial macrophages, both PC and DPPC reversed the inhibitory effect of SP-A on mean(s.d.) LPS-induced carbon monoxide generation (LPS + SP-A + DPPC 4·4(0·3) *versus* 3·3(0·1) for LPS + SP-A and 5·6(0·03) for LPS; $n = 10$, $P < 0.01$) and cGMP increase (LPS + SP-A + DPPC 0·3(0·02) *versus* 0·1(0·01) for LPS + SP-A and 0·3(0·02) for LPS; $n = 10$, $P < 0.01$). These effects were less evident in alveolar macrophages.
Conclusion: Surfactant phospholipids may have a role in modulating the carbon monoxide production by human pulmonary macrophages, although they do not modify cytokine production.

Prospective randomized trial of preoperative immunonutrition in well nourished patients undergoing major surgery for gastrointestinal cancer

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Background: Extensive research suggests that perioperative administration of enteral formula enriched with specific nutrients (immunonutrients) may affect the host's immune and inflammatory responses and improve outcome compared with standard enteral feeds. This study was designed to determine whether simple preoperative immunonutrition in patients undergoing major surgery might exert benefits compared with conventional treatment (no artificial nutrition).

Methods: A prospective trial was undertaken in 304 patients with preoperative weight loss of less than 10 per cent and histologically proven gastrointestinal cancer. Patients were randomized to three groups to receive: (1) oral supplementation for 5 days before operation with 1 litre per day of a formula enriched with arginine, n-3 fatty acids and RNA; no nutritional support was given after operation (preoperative group); (2) the same preoperative treatment followed by postoperative nutritional support (via jejunal infusion) with the same enriched formula until resumption of oral food intake (perioperative group); (3) regular and *ad libitum* food before and after operation as tolerated (control group).

Results: The three groups were comparable for baseline characteristics (age, sex, weight, haemoglobin, Karnofsky index, nutritional parameters, type and duration of operation, blood loss and rate of transfusion). There were 13 patients (13 per cent) with infectious complications in the preoperative group, 16 (16 per cent) in the perioperative group and 30 (30 per cent) in the control group ($P < 0{\cdot}05$ control *versus* preoperative and perioperative groups). The number of patients with non-infectious complications was 24 (24 per cent), 25 (25 per cent) and 32 (32 per cent) respectively (P not significant). The mean(s.d.) length of postoperative stay was 11·8(5·1) days in the preoperative group, 12·2(4·3) days in the perioperative group and 14·0(8·1) days in the control group ($P < 0{\cdot}05$ control *versus* preoperative and perioperative groups; analysis of variance or χ^2 test as appropriate). Forty-six patients in the perioperative group experienced enteral feeding-related side-effects.

Conclusion: Preoperative and perioperative supplementation with an immune-enhancing nutritional formula are equally effective in improving outcome. Both strategies appear to be superior to a conventional approach. Preoperative treatment avoids the complications of postoperative enteral feeding and may reduce costs compared with perioperative administration.

Prospective comparison of antibiotic usage in paediatric surgical patients: safety, advantage and effectiveness of Surgical Infection Society guidelines *versus* common practice

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Background: The Surgical Infection Society (SIS) guidelines for antibiotic usage involve a minimal change in surgical practice. It was hypothesized that clinical evidence for the safety, advantage and effectiveness of the SIS guidelines may improve inappropriate usage of antibiotics.

Methods: A group of dedicated surgeons attempted to use antibiotics appropriately in accordance with SIS guidelines in their patients (group 1). A comparison was made with a concurrent cohort of patients (group 2), treated by surgeons who were non-supporters of the SIS guidelines. The trial was conducted in 375 children between March 1999 and May 2000. Outcome measures were morbidity and mortality, duration of antibiotic treatment, timing of administration, unjustified spectrum and switch of antibiotics. Analysis of variance, χ^2 test and the Mann–Whitney U test were used for statistical analysis. $P < 0{\cdot}05$ was considered significant.

Results: There were 124 patients in group 1 and 251 in group 2. There were no intergroup differences in age, sex and clean/contaminated/dirty ratio of procedures. The mean duration of antibiotic treatment was 3·9 days in group 1 compared with 7·1 days in group 2 ($P < 0{\cdot}05$), with an overall rate of appropriateness of 77 *versus* 36 per cent ($P < 0{\cdot}05$) and no differences in mortality and morbidity.

Conclusion: These results may affect antibiotic usage in paediatric surgery.

Aerosolized hypertonic saline attenuates lung injury due to pancreatitis

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Background: The immunomodulatory effects of hypertonic saline (HTS) provide potential strategies to attenuate inappropriate inflammatory reactions. This study tested the hypothesis that administration of intratracheal aerosolized HTS modulates the development of lung injury in pancreatitis.

Methods: Pancreatitis was induced in 24 male Sprague–Dawley rats by intraperitoneal injection of 20 per cent L-arginine (500 mg per 100 g body-weight). At 24 and 48 h, intratracheal aerosolized HTS (7·5 per cent sodium chloride, 0·5 ml) was administered to eight rats, while a further eight received 0·5 ml aerosolized normal saline. At 72 h pulmonary neutrophil infiltration (myeloperoxidase activity) and endothelial permeability (bronchoalveolar lavage and wet : dry weight ratios) were assessed. In addition, histological assessment of representative lung tissue was performed by a blinded assessor. In a separate experiment, polymorphonuclear neutrophils (PMNs) were isolated from human donors and exposed to increments of HTS. Neutrophil apoptosis and transmigration across an endothelial cell layer were assessed at 1, 6, 12 and 18 h.

Results: Pulmonary neutrophil sequestration (mean(s.d.) 1·4(0·2)) and increased endothelial permeability (6·8(1·1)) were evident in the animals resuscitated with normal saline ($P = 0{\cdot}02$). However, both parameters were significantly reduced in the HTS groups ($P < 0{\cdot}04$). Lung injury scores were significantly diminished in the HTS group (4·8(1·4) *versus* 8·6(0·9); $P = 0{\cdot}02$). HTS significantly reduced PMN transmigration (by 97 per cent; $P = 0{\cdot}002$) and induced PMN apoptosis ($P < 0{\cdot}03$).

Conclusion: Intratracheal aerosolized HTS attenuates the neutrophil-mediated pulmonary insult subsequent to pancreatitis, and this may represent a novel therapeutic strategy.

Cytokine and polymorphonuclear neutrophil elastase release in filtered and non-filtered drained blood

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Background: In orthopaedic surgery, blood drained after operation contains pro-inflammatory mediators such as activated complement factors and cytokines. This study investigated the role of leucocyte filtering on the release of pro-inflammatory cytokines and polymorphonuclear neutrophil (PMN) elastase in drained blood stored for 24 h.

Methods: Postoperative blood from nine patients undergoing major orthopaedic surgery of the spine or the hip joint was drained in two cans, one leucocyte filtered and the other not. The cans were stored for 24 h at a room temperature of 21°C. Interleukin (IL) 1β, IL-6, IL-8, IL-10 and PMN elastase were analysed by means of enzyme-linked immunosorbent assay.

Results: See table below.

Conclusion: This study shows increased release of IL-8 and PMN elastase in unfiltered drained blood stored at room temperature. This effect was absent in filtered blood. It is suggested that the increased concentration of PMN elastase and the cytokines IL-1β, IL-6, IL-8 and IL-10 in drained blood is part of a local inflammatory process in the wound. It seems that leucocytes express mainly IL-8 and PMN elastase when stored at room temperature.

Results:

	Unfiltered blood		Leucocyte-filtered blood	
	At wound closure	At 24 h	At wound closure	At 24 h
WCC (10^9 litre^{-1})	5·8(2·7)	7·7(4·1)	0·2(0·2)	0·2(0·1)
IL-1β (pg ml^{-1})	1·7(2·6)	1·7(2·4)	1·5(2·5)	1·5(2·3)
IL-6 (pg ml^{-1})	2266(1362)	2214(1215)	2218(1289)	2204(1247)
IL-10 (pg ml^{-1})	15(7·5)	15(9·6)	15(9·3)	17(11)
IL-8 (pg ml^{-1})	497(378)	3898(2492)*	491(367)	518(404)
PMN elastase (μg l^{-1})	105(71)	149(65)*	117(55)	103(53)

Values are mean(s.d.). WCC, white cell count. *$P < 0{\cdot}05$ *versus* wound closure (analysis of variance)

Involvement of CD14 and toll-like receptors in signalling by *Aspergillus* hyphae

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Background: Invasive fungal infections represent an increasing problem associated with a high mortality rate. The present study was undertaken to examine the involvement of CD14 and toll-like receptors (TLRs) in the activation of monocytes by *Aspergillus* hyphae.

Methods: Primary adherent human monocytes were pretreated with different concentrations (1, 3 and 10 μg ml^{-1}) of monoclonal antibody (mAb) TL2.1 (anti-TLR2), mAb HTA125 (anti-TLR4) or mAb 18D11 (anti-CD14) for 30 min, followed by the addition of hyphal fragments. After 6 h, supernatants were isolated and analysed for tumour necrosis factor (TNF) α by enzyme immunoassay.

Results: Pretreatment with mAb HTA125 (anti-TLR4) or mAb 18D11 (anti-CD14) inhibited the release of TNF-α in a dose-dependent manner. A maximal inhibition of 35 and 70 per cent was obtained with 10 μg ml^{-1} of HTA125 and 18D11 respectively. In contrast, pretreatment with mAb TL2.1 (anti-TLR2) did not affect signalling induced by hyphae. Pretreatment with the lipid A antagonist B975 blocked lipopolysaccharide signalling, but did not inhibit TNF-α production induced by hyphal fragments.

Conclusion: These results suggest that CD14 and TLR4, but not TLR2, mediate signalling events induced by *Aspergillus* hyphae in monocytes.

Epidural catheter infection and associated factors

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Background: Epidural anaesthesia has been used widely in patients undergoing surgery or obstetric care. Localized infection, epidural abscess and infection of the central nervous system (CNS) following the placement of an epidural catheter are potential complications.

Methods: Over a period of 18 months the incidence of bacterial contamination after epidural catheterization, at the lumbar site, was investigated in 85 adult patients (32 men, 53 women) having surgical or obstetric operations under epidural anaesthesia. The mean(s.d.) duration of catheter placement was 2·9(0·2) days.

Results: Bacteriological analysis of the 85 epidural catheters showed a positive culture in 28 per cent. Of these, only two were polymicrobial. The commonest micro-organism found was *Staphylococcus epidermidis* (58 per cent). Neither CNS nor systemic infections occurred during the study interval. No correlation was found between the type of operation, type of antimicrobial prophylaxis, sex or age of patients, duration of catheter placement, maximum body temperature or the incidence of positive cultures.

Conclusion: Although a mean duration of catheter placement of less than 3 days is associated with a catheter positive culture rate of 28 per cent, this does not represent a risk factor for CNS or systemic infections.

Relation of *TNF* gene polymorphism to postoperative production of tumour necrosis factor α

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Background: Individual genetic risk factors and postoperative immunosuppression may result in complications after major abdominal operations. Polymorphism of the tumour necrosis factor (TNF) β gene already has been shown to be associated with severe sepsis in trauma patients. The aim of this study was to relate this polymorphism to the TNF-α production of lipopolysaccharide (LPS)-stimulated whole blood in patients with and without postoperative complications.

Methods: Ninety patients undergoing major abdominal surgery were typed for TNF-β gene polymorphism by analysing restriction fragments of a *Nco*I-digested DNA fragment obtained using the polymerase chain reaction. Before operation and repeatedly during the postoperative course, whole blood from the patients was stimulated *ex vivo* with LPS and production of TNF-α was determined.

Results: The postoperative morbidity rate was 19 per cent, resulting in a 3 per cent mortality rate. The whole blood of *TNFB2* homozygous patients produced significantly less TNF-α at day 7 than that of patients with the *TNFB1/B2* or *TNFB1/B1* genotype. A complicated clinical course was associated with significantly lower TNF-α production in the whole blood at days 3 and 7.

Conclusion: These data suggest an association between the *TNFB2/B2* genotype and a low postoperative TNF-α production. This was due to the low production of TNF-α in patients in the *TNFB2/B2* group who had complications. The study is continuing to assess the relation between the *TNFB2/B2* genotype and postoperative complications.

Inhibition of melvalonate production attenuates endotoxin-mediated microvascular leakage

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Background: An early critical event in sepsis or endotoxin-mediated tissue injury is the interaction between leucocytes and endothelium, mediated by adhesion molecules on the vascular endothelium and involving a three-stage process: rolling, adhesion and, finally, transendothelial migration. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors have anti-inflammatory and vascular effects independent of their serum lipid-lowering properties. They increase the bioavailability of nitric oxide, a molecule that downregulates adhesion receptors. The aim of this study was to determine whether pravastatin would attenuate endotoxin-mediated microvascular leakage.

Methods: Male Sprague–Dawley rats were randomized into control, lipopolysaccharide (LPS), and pravastatin plus LPS groups (seven animals in each group). Pravastatin was gavaged at 4 mg kg^{-1} daily over the preceding 5 days. LPS 15 mg kg^{-1} was administered via the jugular vein after baseline recording. Using intravital microscopy, leucocyte rolling, adhesion and migration were measured at baseline, 10, 30, 60 and 90 min in mesenteric postcapillary venules. Data are expressed as mean (s.e.m.); analysis of variance and the *post hoc* Scheffé test were used.

Results: Results at 60 min are given in the *Table*.

	Control	LPS	Pravastatin +LPS
Leucocyte rolling velocity (µm s^{-1})	186·7(11·6)*	55·2(4·4)	135·5(15·3)*
Leucocyte adhesion (per 100 µm)	3·0(0·2)*	11·0(2·0)	4·0(0·6)*
Transendothelial migration (per field)	1·6(0·2)*	5·2(0·3)	2·2(0·2)*

*$P < 0·05$ *versus* LPS group at 60 min (analysis of variance)

Conclusion: These data indicate that inhibition of melvalonate production attenuates endotoxin-mediated microvascular injury by maintaining leucocyte rolling velocity, while decreasing leucocyte adhesion and migration. A possible mechanism of action involves the upregulation of constitutive endothelial nitric oxide synthase, which increases the bioavailability of the anti-inflammatory molecule, nitric oxide.

Primary anastomosis after sigmoid resection for diverticulitis is a safe procedure

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Background: Primary anastomosis after colonic resection for sigmoid diverticulitis remains controversial. The risk of anastomotic leakage is considered to be high by many authors and therefore secondary reconstruction is still recommended.

Methods: This retrospective review analysed all patients operated on for acute sigmoid diverticulitis between 1979 and 1999. The surgical concept favoured primary anastomosis, but operating surgeons were free to perform resection alone or an additional protective stoma or a Hartmann procedure, depending on their judgement of the intraoperative situation. A total of 130 patients (47 men, 83 women) with a mean age of 64·5 (range 20–91) years underwent surgery. Diverticulitis was classified according to Hinchey: 81 patients (62 per cent) were classified as having stage I disease, 35 (27 per cent) as stage II, ten (8 per cent) as stage III and four (3 per cent) as stage IV. Data on mortality, morbidity and operative procedure were analysed.

Results: In 124 patients (95 per cent) resection and primary anastomosis was performed, on two occasions with a protective transverse colostomy; four patients (3 per cent) had a Hartmann procedure, a single patient underwent abdominoperineal resection, and one was treated by local suture and drainage. Three patients (2 per cent) died from septic multiorgan failure; all had stage IV disease. The procedure undertaken in these patients had been abdominoperineal resection, Hartmann procedure and primary anastomosis. No patient died from an anastomotic complication. The overall morbidity rate was 17 per cent ($n = 22$) and consisted of anastomotic leakage (two patients), intraperitoneal bleeding (four), ileus (one), pulmonary embolism (four), antibiotic-associated colitis (two), cardiac failure (three), pneumonia (one), wound infection (three), epididymitis (one) and urinary infection (one). Two anastomotic leakages (2 per cent) occurred; both were treated successfully by protective stoma and drainage.

Conclusion: Primary anastomosis after sigmoid resection for acute diverticulitis is a safe procedure. Mortality and morbidity were not related to operative procedures but to the stage of diverticulitis.

Methicillin-resistant *Staphylococcus aureus* colonization and infection following antimicrobial prophylaxis and therapy: results of infection control management

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Background: The aim of the study was to evaluate a risk profile for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and to determine the success of isolation and treatment.

Methods: All patients diagnosed with MRSA between 1 January 1994 and 31 December 1999 were investigated retrospectively, including history, previous medication, and microbiological and clinical course. After isolation of MRSA, the patients were isolated strictly and treated by chlorhexidine washing and application of nasal mupirocin ointment. Since 1 January 1996 only a MRSA infection was treated with vancomycin, and surgery was performed only in emergency cases.

Results: In 98 cases (55 men, 43 women) MRSA was isolated. The mean age was 66·7 years. Most frequently associated factors were previous antimicrobial administration (95 patients), hospital stay over 28 days (78) and malignancy (36). MRSA was isolated mainly from wound sites (66), skin (43) and tracheal aspirates (26). The incidence declined from 31 in 1996 to 13 in 1999. Twenty-five patients died, seven as a result of MRSA infection (pneumonia, four patients; septicaemia, two; thoracic empyema, one). The infection was eradicated in 39 patients; 34 patients developed MRSA colonization.

Conclusion: Antibiotic prophylaxis was the most common risk factor in patients with MRSA. By standardized isolation and treatment criteria a reduction in the number of cases could be achieved. Only MRSA infection calls for antibiotic treatment.

Autologous transfusion of drained blood delivers a load of inflammatory mediators

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Background: The aim of this study was to examine the inflammatory mediators released during autologous transfusion with unwashed blood drained after operation.

Methods: In nine patients subjected to major orthopaedic surgery of the thoracic spine, 10 ml kg^{-1} of blood drained after operation was infused for 1 h. Samples were drawn concomitantly from a peripheral arterial cannula and a pulmonary arterial catheter before operation (control), and before, during and after the infusion. Tissue factor (TF) apoprotein, interleukin (IL) 1β, IL-6, IL-8, IL-10 and tumour necrosis factor (TNF) α were analysed with enzyme-linked immunosorbent assay kits.

Results:

	Infusion of unwashed blood				
	Control	Before	During	After	Drained
TF (pg ml^{-1})					
Arterial	127·9(75)*	39·6(38)	95·7(49)*	63·5(45)	
Mixed venous		39·7(44)	78·2(46)*	56·4(47)	773(353)*
IL-6 (pg ml^{-1})					
Arterial	0·8(1·7)*	107(57)	280(57)*	121(47)	
Mixed venous		108(58)	357(143)*	112(41)	14 078(10 039)*
IL-10 (pg ml^{-1})					
Arterial	3·4(4·3)*	71(62)	18(27)*	26(24)*	
Mixed venous		72(74)	26(34)*	45(35)	19(19)*

Values are mean(s.d.). *$P < 0.05$ *versus* before infusion value (analysis of variance)

Conclusion: Autologous transfusion of unwashed drained blood delivers a heavy load of inflammatory mediators to the circulation. The level of TF apoprotein was reduced in circulating blood after major orthopaedic surgery, in spite of the increased amount in drained blood indicating profound activation in the wound. The reduction of IL-10 concentration during infusion might be an unwanted effect as IL-10 is thought to reduce inflammation. The IL-6 concentration increased during infusion, but not to expected levels. This indicates a tight regulation of the level of IL-6. In spite of this heavy load of cytokines and proinflammatory compounds, only one patient suffered rigors and pyrexia.

Quality of life and the McPeek recovery index as a new outcome concept for sepsis trials tested in a pilot study of granulocyte colony-stimulating factor in patients with colorectal cancer

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Background: The consensus-assisted development of a study protocol by an international study group for a granulocyte colony-stimulating factor (G-CSF) prophylaxis trial in surgical patients at high risk for an adverse outcome identified the need for a new outcome concept. An endpoint construct was developed consisting of quality of life (QoL) and a recovery index (modified McPeek index).

Methods: In a pilot trial, QoL was measured in five patients at hospital discharge, and 2 and 6 months after operation with the EORTC-QLQ-C30 (European Organisation for Research on Treatment of Cancer – Quality of Life Query – C30). From each patient a QoL profile was drawn at the three points of measurement including somatic, psychological and social dimensions. The modified McPeek index represents the speed of postoperative recovery and ranges from 0 (death in the operating theatre) to 9 (discharge as predicted and without additional intensive care). The comprehensibility of the QoL profiles was tested in a survey including 24 practitioners involved in cancer patient care.

Results: All practitioners participating in the survey indicated that the QoL profile was highly understandable and useful in practice. With regard to comprehensibility, the McPeek index has high face validity because of the use of nominal scaling and labelling of the ten categories in everyday clinical vocabulary. In the pilot trial two patients had global QoL scores greater than 50 (an acceptable level) 6 months after operation. Three patients scored less than 50 (0, 20 and 30 points). Two of the patients with low QoL scores never approached a score above 30 in the course of the observation period. One patient's score decreased from 75 (at discharge) to 20 points (6 months after operation). The McPeek index evidenced a parallel data pattern: patients with high QoL scores scored 8 and 4 McPeek points, and those with low QoL scores had 2, 4 and 4 McPeek points.

Conclusion: These results confirm the comprehensibility and variance of the selected outcome measures. Therefore, this outcome concept is highly likely to detect possible benefits for G-CSF prophylaxis in high-risk patients with colorectal cancer.

Secondary infection of pancreatic necrosis during operative treatment of necrotizing pancreatitis does not increase the mortality rate

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Background: Surgery for sterile pancreatic necrosis is the subject of debate. One argument against necrosectomy is the possible secondary infection of sterile necrosis.

Methods: Some 267 patients operated on for necrotizing pancreatitis since 1978 were reviewed with regard to patient characteristics and type of infection. Logistic regression was employed to identify risk factors for death.

Results: Some 75 patients (28 per cent) had no infection (NI), 85 (32 per cent) had primary infection (at first necrosectomy) (PI) and 107 (40 per cent) had secondary infection (SI) of pancreatic necrosis. The mean(s.e.m.) age of the groups was 50(2) years (NI), 56(2) years (PI) and 50(2) years (SI) ($P < 0.01$). Patients were first operated on a mean(s.e.m.) of 17(4) days (NI), 19(2) days (PI) and 10(2) days (SI) after onset ($P < 0.03$). The mean(s.e.m.) number of operations was 1·2(0·2) (NI), 2·5(0·4) (PI) and 3·8(0·4) (SI) ($P < 0.01$). The mean(s.d.) Acute Physiology And Chronic Health Evaluation (APACHE) II score was 12(0·6) (NI), 17(0·9) (PI) and 15(0·7) (SI) ($P < 0.01$). Necroses were found to be infected with enterococci, enterobacteria and *Candida* in 88 per cent of patients with PI, compared with 79 per cent of those with SI. The in-hospital mortality rate for the three groups was 14, 56 and 32 per cent for patients with NI, PI and SI respectively. Logistic regression revealed the following factors as independent prognosticators of mortality: age (relative risk (RR) 1·06 (95 per cent confidence interval (c.i.) 1·03–1·09)), APACHE II score (RR 1·2 (95 per cent c.i. 1·1–1·3)), extension of necrosis (less than 50 per cent, 50 per cent or more) (RR 2·3 (95 per cent c.i. 1·1–4·8)) and PI (RR 4·3 (95 per cent c.i. 1·7–11·2)). SI (RR 2·0 (95 per cent c.i. 0·7–5·2); $P = 0.2$) was not an independent prognostic factor for death.

Conclusion: Essentially the same bacteria are cultivated from patients with secondary infection as from those with primary pancreatic necrosis. A similar mechanism of infection by intestinal translocation is therefore as conceivable as infection as a result of surgery. Secondary infection of debrided pancreatic necrosis, however, does not seem to affect mortality significantly.

Hepatoprotection by gadolinium chloride during early endotoxaemia in an experimental model

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Background: Kupffer cells are key contributors in the systemic inflammatory response associated with sepsis. Blockade of the activity of these cells by gadolinium chloride protects rodents from the lethality of sepsis. This study evaluated the effect of gadolinium chloride on the response to infusion of endotoxin in a porcine model.

Methods: Juvenile pigs were randomized to receive either gadolinium chloride 10 mg kg^{-1} ($n = 8$), 30 mg kg^{-1} ($n = 8$) or an equivalent volume of acidic saline intravenously ($n = 8$) 24 h before the experiments. Catheters and flow probes were inserted under general anaesthesia. After a recovery period, endotoxin 1·7 µg kg^{-1} h^{-1} was infused continuously through a mesenteric vein over 5 h. Venous and arterial pressure, and hepatic arterial and portal venous flow, were monitored continuously. Blood specimens were obtained for analysis of leucocyte count, blood gases and biochemistry.

Results and conclusion: Gadolinium chloride significantly reduced hepatic oxygen consumption and extraction ratio in response to early (1–3 h) endotoxinaemia in a dose-dependent manner. Gadolinium chloride 30 mg kg^{-1} abolished the increase in hepatic arterial flow seen at 2 h and the increase in the serum level of alanine aminotransferase seen after 5 h in untreated animals. There was, however, a gradual decrease in portal venous flow and cardiac output in both test animals and controls.

Early interleukin 10 treatment following haemorrhage: reversal of the sex-related effect with ageing

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Background: Early interleukin (IL) 10 treatment has been shown to have beneficial effects on the immune function of young male mice, but not that of young females following haemorrhagic shock. Although it was demonstrated that the immune function under these conditions is reversed with age, it remains unclear whether the observed sex-related effect of IL-10 treatment continues with age.

Methods: To study this, older male and female CBA/J mice (eight per group; age 18–19 months) were subjected to haemorrhage (mean(s.d.) 35(5) mmHg for 90 min and fluid resuscitation). At resuscitation, each animal received either recombinant murine IL-10 or placebo i.o. At 48 h after resuscitation, splenic macrophages and splenocytes were harvested. IL-6 and tumour necrosis factor (TNF) release of macrophages, as well as splenocyte IL-2 and interferon (IFN) γ release capacity, were assessed.

Results: With age, females lost their enhanced immune function following haemorrhage with decreased TNF or unchanged proinflammatory cytokine release. IL-10 treatment restored depressed TNF release and enhanced IL-2, IL-6 and IFN-γ response in older females following haemorrhage. However, IL-10 treatment of sham-operated female and male mice led to immune depression in comparison with placebo-treated animals. In contrast, the immune responses in older males receiving IL-10 were unchanged following haemorrhage.

Conclusion: Early IL-10 anti-inflammatory treatment after haemorrhage in older mice reversed the sex-related effects observed in young mice, with potential beneficial effects in females but not in males.

Quantification of chemokine release in human mesothelial cells under the influence of various bacteria

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Background: To evaluate the clinical relevance of bacteria frequently causing peritonitis, release of the chemokine interleukin (IL) 8 from human peritoneal mesothelial cells (HPMCs) was measured after stimulation with lysates of Gram-negative, Gram-positive and anaerobic bacteria.

Methods: HPMCs were isolated from human omental tissue by treatment with trypsin and cultivated to confluent monolayers. Bacteria (*Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Propionibacterium acnes, Salmonella paratyphi, Proteus mirabilis*) were sonicated and supernatants were added to HPMC cultures in two concentrations, 10 and 100 µg ml^{-1}. To assess the influence of particular bacterial subcompartments, lipopolysaccharide (LPS) from *E. coli* and *P. aeruginosa*, and peptidoglycan and lipoteichoic acid from *S. aureus*, were used. IL-8 concentration was measured by chemiluminescence at four different timepoints (before and 1, 6 and 24 h after stimulation).

Results: Gram-negative bacteria induced IL-8 production by HPMCs in a time- and concentration-dependent manner. IL-8 release following stimulation with Gram-positive and anaerobic bacteria could not be detected. Responses to different Gram-negative bacterial species varied significantly.

Conclusion: LPS, but not peptidoglycan or lipoteichoic acid, induced IL-8 release in a similar amount to that following stimulation with Gram-negative bacteria.

Relative hyperoxia augments lipopolysaccharide-stimulated tumour necrosis factor secretion by RAW 264.7 macrophages

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Background: Inflammatory cytokines are increased following open abdominal operations and intra-abdominal sepsis. Macrophages exposed to lipopolysaccharide (LPS) become activated and release cytokines, such as tumour necrosis factor (TNF). Peritoneal macrophages are normally exposed to an arterial partial pressure of oxygen ($Pa\text{O}_2$) of about 45 torr (6 kPa). It was hypothesized that exposure of LPS-stimulated macrophages to a 'non-physiological' $Pa\text{O}_2$ exacerbates inflammation.

Methods: RAW 264.7 macrophages were preconditioned to a $Pa\text{O}_2$ of approximately 45 torr for 24 h. Medium was discarded and then exchanged for a medium preconditioned to a $Pa\text{O}_2$ of about 45, 150 or 440 torr (6, 20 and 59 kPa respectively). Cultures were incubated at the desired $Pa\text{O}_2$ for 6 h, during which time they were stimulated with LPS 0–100 ng ml^{-1}. The effect of $Pa\text{O}_2$ was compared. The $Pa\text{O}_2$ of the medium was measured at the end of the stimulation interval. Supernatant TNF concentration was measured by means of enzyme-linked immunosorbent assay. Statistical analysis was performed with analysis of variance.

Results: Dose-dependent LPS-stimulated TNF production was stimulated in macrophages incubated at a physiological $Pa\text{O}_2$. Higher $Pa\text{O}_2$ alone did not stimulate TNF release without LPS. However, $Pa\text{O}_2$ of 150 and more than 400 torr significantly enhanced (twofold to threefold increase) LPS-stimulated TNF production ($P < 0{\cdot}001$).

Conclusion: These data suggest synergy between $Pa\text{O}_2$ and LPS for macrophage TNF production. A similar increase in $Pa\text{O}_2$ may occur with open peritoneum or high supplemental oxygen. Cytokines from peritoneal macrophages may contribute to the pathogenesis of sepsis and systemic inflammatory response syndrome.

Low-dose subcutaneous interleukin 2 prophylaxis in an experimental model is effective in decreasing mortality from sepsis

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Background: Recent data show that immunoprophylaxis with intraperitoneal administration of interleukin (IL) 2 improves survival in septic rats undergoing caecal ligation and puncture (CLP) (mortality rate 33 per cent *versus* 70 per cent if treated with antibiotics alone). The aim of this study was to investigate whether subcutaneous administration of IL-2 might similarly reduce the mortality rate and to determine the minimum effective dose of IL-2 needed to prevent death.

Methods: Peritonitis was induced by CLP in rats weighing 250–300 g. Preoperative administration of IL-2 was intraperitoneal in group 1 and subcutaneous in group 2 (IL-2 dose 3 000 000 units kg^{-1}). Animals in group 3 had subcutaneous preoperative IL-2 administration at a dosage of 900 000 units kg^{-1}; those in group 4 were treated with 300 000 units kg^{-1}; and animals in groups 5 and 6 received 90 000 and 30 000 units kg^{-1} respectively. All groups received antibiotic therapy (amikacin and clindamycin). Death within 72 h of CLP was monitored.

Results: Animals in groups 1 and 2 had a similar mortality rate (28 *versus* 37 per cent respectively; $P = 0{\cdot}64$). Group 3 animals had a mortality rate of 31 per cent, and in group 4 the mortality rate was reduced to 19 per cent ($P = 0{\cdot}68$). In groups 5 and 6 the mortality rate was increased to 50 per cent.

Conclusion: IL-2 is not only effective after local injection, but systemic administration also primes host defences. The minimum effective dose ranges between 90 000 and 300 000 units kg^{-1}, which is comparable to the clinical oncological schedule.

Learning period in laparoscopic colorectal surgery: impact on postoperative infections and outcome

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Background: The aim was to evaluate the impact of a 6-month learning period in laparoscopic colorectal surgery (LCS) on postoperative infections and outcome. Before beginning the study the surgical team attended several courses on LCS and spent a long time in a large animal facility perfecting laparoscopic techniques.

Methods: Between July and December 1999, 26 consecutive patients underwent LCS by the same surgical team (group 1). A statistician unaware of postoperative outcome identified 26 matched control patients who underwent open colorectal surgery (group 2) before June 1999 by using a prospectively gathered database that had been in use in the authors' department since 1994. Matching features were age, primary disease and type of operation. In the case of two or more matching patients the control was chosen according to sex, co-morbidity at admission (American Society of Anesthesiologists (ASA) score) and nutritional status.

Results: Conversion to open operation was necessary in one of the 26 patients. In group 1, the mean(s.d.) operating time was longer than that in group 2 (206·2(50·9) *versus* 148·8(48·4) min; $P = 0{\cdot}001$). The mean number of lymph nodes collected was 17 in the 20 patients with cancer in group 1 and 18 in the 20 with cancer in group 2 ($P = 0{\cdot}56$).

No perioperative death occurred in either group. In patients who had LCS, passage of flatus occurred earlier (2 *versus* 3 days; $P = 0{\cdot}002$), as did return of defaecation (5 *versus* 6 days; $P = 0{\cdot}33$). Two anastomotic leaks occurred in each group. The mean(s.d.) postoperative hospital stay was 9·6(2·6) days in group 1 and 11·0(5·2) days in group 2 ($P = 0{\cdot}6$).

Conclusion: Despite the learning period, the laparoscopic technique allowed a faster recovery of gastrointestinal function and a trend towards fewer postoperative infections and shorter postoperative stay.

Monitoring of interleukin 6, interleukin 10, tumour necrosis factor α and procalcitonin in addition to conventional parameters in the detection of postoperative complications after major abdominal surgery

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Klinik und Poliklinik für Allgemeinchirurgie, Halle/Saale, Germany

Background: This study compared the accuracy of detecting postoperative complications by monitoring levels of tumour necrosis factor (TNF) α, interleukin (IL) 6, IL-10 and procalcitonin (PCT) compared with the conventional parameters of white blood cell count (WBC) and C-reactive protein (CRP) concentration.

Methods: Between February and April 1999, in 35 patients undergoing major abdominal surgery, the levels of cytokines and PCT were measured every 2 h after the start of the operation and daily from the first postoperative day. IL-6, TNF-α and IL-10 were determined by means of IMMULITE® (DPC, Bad Nauheim, Germany) and PCT was measured using a chemoluminescence test (PCT LUMI®, Brahms, Berlin, Germany). CRP and WBC were recorded from patients' charts.

Results: All parameters showed a continuous decrease once they reached certain peak values induced by the surgical trauma. In patients with postoperative complications there was a second increase in the phase where the values were consecutively declining. This second increase in TNF-α, PCT and IL-6 levels provided better diagnostic accuracy than WBC and CRP (sensitivity 80 *versus* 40 per cent; specificity 95 *versus* 71 per cent; positive predictive value 83 *versus* 46 per cent; negative predictive value 95 *versus* 89 per cent). Specificity almost reached 100 per cent when two or three markers were combined, although this led to large decreases in sensitivity.

Conclusion: Levels of TNF-α, IL-10 and PCT should be measured in high-risk patients undergoing major abdominal surgery.

Is bacteriological screening mandatory after outbreaks of methicillin-resistant *Staphylococcus aureus* in the surgical intensive care unit?

K.-H. Staubach, R. Bouchard, C. Eckmann and P. Kujath
Department of Surgery, Medical University of Lübeck, Lubeck, Germany

Background: Knowledge of clinical microbiology and close co-operation between intensive care unit (ICU) physicians and microbiologists is advisable. Methicillin-resistant *Staphylococcus aureus* (MRSA) nosocomial infections associated with a high infection-related morbidity rate are becoming an increasing problem.

Methods: After two spontaneous cases of MRSA infection in the authors' surgical ICU (12 beds), screening of all operating and nursing staff in the department of surgery was carried out. In a first step nasal swabs were taken, and in case of bacterial colonization swabs from the skin were added.

Results: Of 60 doctors, 15 (25 per cent) had a positive nasal swab of non-resistant staphylococcal species; none had colonization of the skin. Twelve (23 per cent) of 52 members of the nursing staff were colonized in the nose and three (6 per cent) had skin colonization with non-resistant staphylococcal species. The highest rate of colonization was found in cleaning staff: four of seven had a positive nasal swab, with one positive swab of the skin. This person remained colonized despite all therapeutic measures. Four of eight physiotherapy staff were nasally colonized, but none had skin involvement. Eradication by therapeutic measures with antistaphylococcal agents was successful in all but one case. None of the staff was a proven carrier of MRSA.

Conclusion: From the point of view of prevention, it may be useful routinely to screen the flora of clinical staff, as 20–25 per cent appear to be colonized with non-resistant staphylococcal species.

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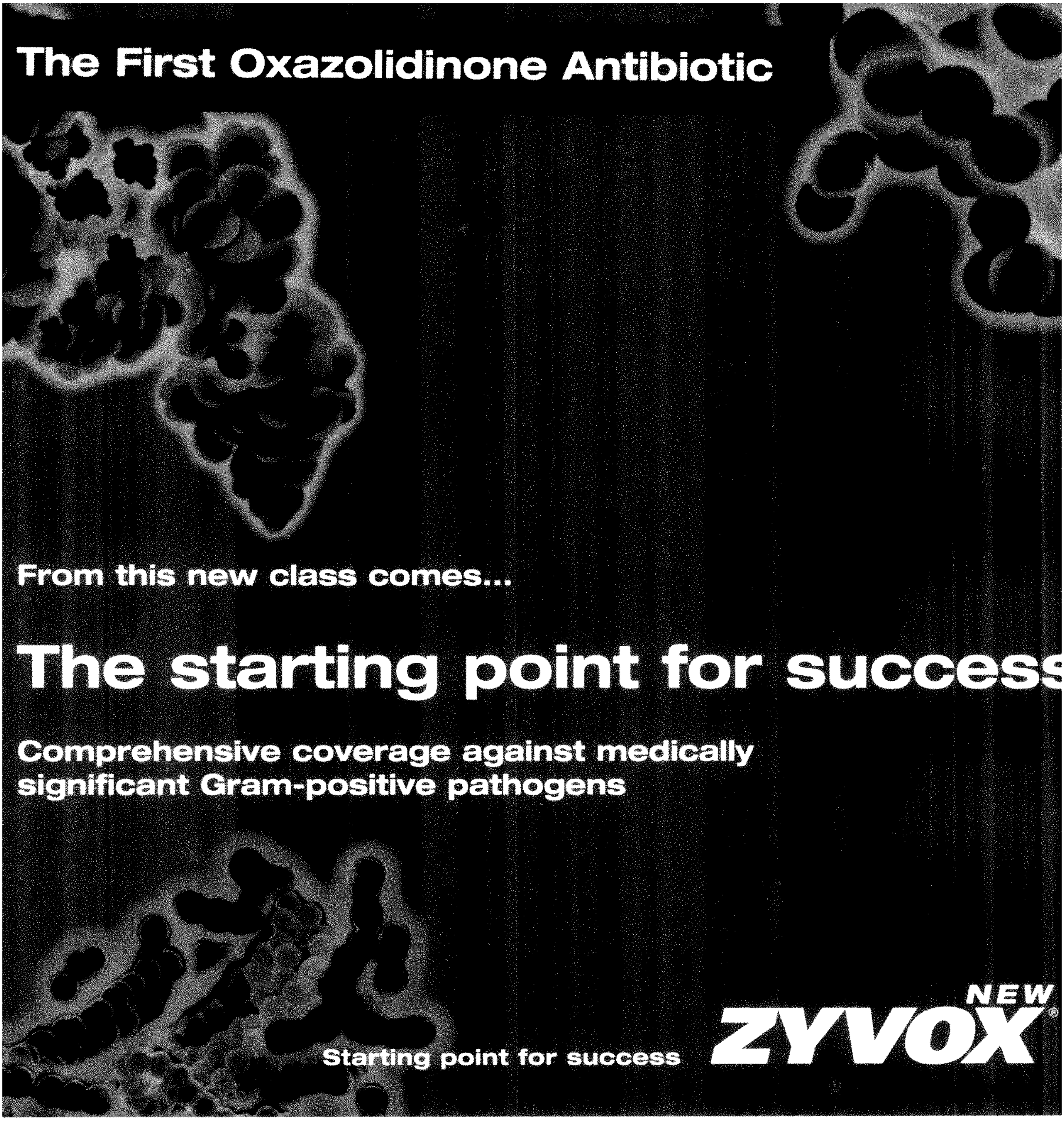
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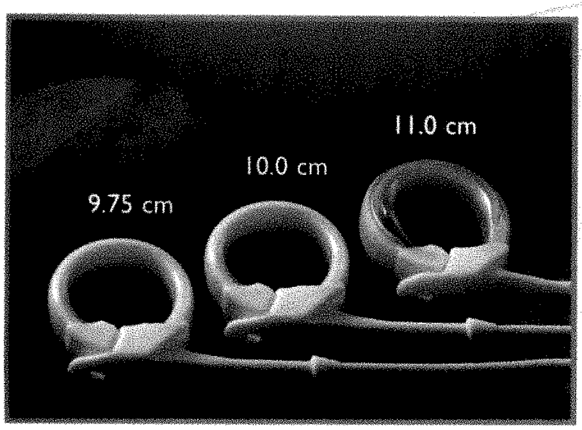

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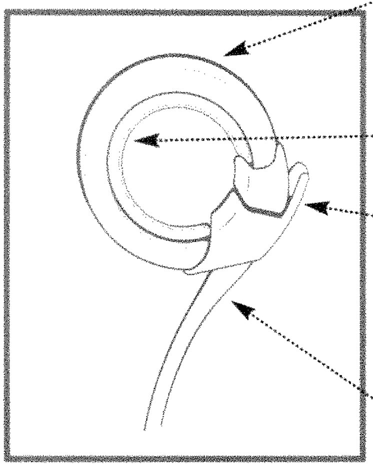

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This is the sixth in a series of articles on ethics, professional governance and the law that BJS *will run through the remainder of 2001.*

Postoperative futility: a clinical algorithm for setting limits

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In *The Art*, the Hippocratic writers justify refusing to 'treat those who are overmastered by their diseases, realizing that in such cases medicine is powerless'[1]. More recently, medicine has considered setting limits on critical care and accession to inappropriate requests for life-sustaining interventions such as mechanical ventilation, parenteral fluids and nutrition, and pharmacological cardiac support. Limit setting now arises routinely in areas of postoperative management when the prognosis is futile[2]. This paper identifies four concepts of futility found in the bioethical and medical literature, and proposes an algorithm for understanding ethically justifiable limits in postoperative critical care.

Four concepts of futility

Futility means that clinical intervention is reliably expected not to have the intended therapeutic effect. Clinical applicability of this definition requires that the desired effect be specified. The first three concepts of futility to be considered appeal to the ethical principle of beneficence for the requisite specification. This ethical principle requires the physician to seek greater benefit than harm for the patient when assessing treatment risks. The key determinant of beneficence in clinical judgements is whether an intervention has potential clinical benefit[3].

Tomlinson and Brody[4] introduced the first beneficence-based concept of futility: physiological or strict futility. An intervention is futile in this sense when it is unlikely to produce physiological benefit. Surgical intervention in a patient with a Glasgow Coma Score of 3 following an intracerebral bleed is strictly or physiologically futile, because there is no realistic expectation that spontaneous brain function can be restored.

Schneiderman *et al.*[5] introduced the second beneficence-based concept of futility: clinical or overall futility. An intervention is futile in this sense when it is unlikely to restore the patient's ability to interact with the environment and continue human development. A patient in a persistent vegetative state has irreversibly lost these capacities[6]. Although interventions such as parenteral nutrition and administration of fluids are physiologically effective, the patient does not benefit.

Brody and Halevy[7] introduced the third beneficence-based concept: imminent demise futility. An intervention is futile in this sense when the patient is reliably expected to die without recovering consciousness before discharge. Two extensive series have shown that all patients who arrested in the field and were not successfully resuscitated on arrival in the emergency department were dead at discharge and seldom recovered consciousness[8,9].

Tomlinson and Brody[4] introduced the fourth concept, qualitative futility, appealing to the ethical principle of autonomy. This principle requires the physician to seek more good than harm from the patient's perspective, which may not be limited to clinical risks and benefits. An intervention is qualitatively futile when it is probable that the quality of life (ability to participate in and enjoy life events) will be unacceptable to the patient. The patient retains the ability to interact with the environment and develop, but judges the result unacceptable. When dealing with this idea it must be acknowledged that an observer's estimation of the patient's quality of life is insufficiently reliable[10]. Applying this concept of futility requires accurate understanding of the patient's preferred activities and expectations of satisfaction. The person best positioned to understand this is the patient; only well informed surrogates should decide for patients no longer able to do so for themselves.

Algorithm for clinical judgements of futility in the postoperative period

In the ethics of the informed consent process, the surgeon must offer information to the patient or surrogate about medically reasonable alternatives. 'Medically reasonable' means that the intervention meets the 'modicum of benefit' test of beneficence-based clinical judgement[3]. Clinical judgements of futility mean that the interventions under consideration, including life-sustaining interventions in the surgical intensive care unit, fail this test. The surgeon should recommend against them and counter requests for them with sensitive but firm resistance. The proposed algorithm for clinical judgements of futility in the postoperative period links the four concepts of futility to the informed consent process, enabling the surgeon to fulfil the physician's fundamental ethical and professional responsibility to protect patients from harm. Referral to ethics consultants or committees can help resistant surrogates to accept physicians' recommendations in each instance.

Step 1: Physiological futility

Will the clinical intervention produce its usually intended physiological effect? If the answer is no, and intervention has not begun, explain why it will be physiologically ineffective and recommend withholding it. If intervention has begun (e.g. intubation and ventilatory support), recommend its discontinuation.

Step 2: Clinical futility

Will the clinical intervention produce clinical benefit, enabling the patient to interact with the environment and develop as a human being? If the answer is no, and intervention has not been started, explain why it will not restore interactive capacity. To surrogates who insist that it is medicine's responsibility unequivocally to resist death, explain that limits on the obligation to preserve life have been accepted in medical ethics throughout history. Empathically explain that withholding or withdrawing fluid and nutritional support is not starvation, and that the inability to take nourishment by mouth is a function of the patient's medical condition. For surrogates unpersuaded by these arguments, consider withholding all other life-sustaining interventions. If intervention is requested, recommend that it be withheld or withdrawn.

Step 3: Imminent demise futility

Will the patient die without regaining consciousness before discharge? If the answer is yes, proceed as in step 2.

Step 4: Qualitative futility

Will the intervention be physiologically and clinically effective, but with significant risk of disease-related or iatrogenic morbidity, loss of function and unacceptable quality of life? If the answer is yes, recommend continuing an intensive care unit management trial to determine whether its results remain consistent with the patient's judgement about an acceptable quality of life. The surgeon should encourage preoperative discussion of the patient's criteria for continuing, withholding or withdrawing life-sustaining interventions.

While deaths following application of this algorithm are anticipated and should be disaggregated from other surgical mortality data, the cases should be reviewed regularly at morbidity and mortality conferences. The algorithm should aid clinicians in making sound clinical ethical judgements about postoperative futility, even when earlier death ensues.

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Confidentiality and healthcare

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It is not possible to do justice to this topic in a relatively short article at a time of such confusion and controversy; the aim, therefore, will be to identify the existing problems and encourage a constructive debate on the important issues. The article will also advocate formal action by the UK Departments of Health to overcome the present highly unsatisfactory position.

While much present concern relates to those aspects of confidentiality of particular relevance to epidemiological research, the establishment and use of registers, and disease surveillance, there has long been concern over the more day-to-day aspects of confidentiality of individual patient records in the clinical setting. This is an area in which action is clearly required to ensure greater security of personal privacy. With respect to research, registers and surveillance, there has been an assumption, since the aims of such activities are greater understanding of disease and improving healthcare, that information for these wider purposes can be used without explicit consent, provided there are clear and appropriate safeguards. Indeed, there have been no formal challenges over such use. However, there has been increasing concern in the UK over the interpretation of both the Data Protection Act[1] and the General Medical Council publication on confidentiality[2], culminating in the political debate linked to clauses in the Health and Social Care Bill this year.

The issues

Perhaps the main underlying concern relates to what is meant by implied and explicit consent, and the circumstances and purposes for which explicit consent is not required. Linked to this, frequently used terms such as sensitive data, pseudoanonymized and anonymized all need to be defined carefully. Although both the Data Protection Act[1] and the Caldicott Report[3] recognize the importance of medical research and disease prevention, and accept that in certain circumstances explicit consent is not always available, the practical implications remain unclear. These are now surfacing, appropriately, for public debate. The areas of interest include: information for registries, information for communicable disease surveillance, small area statistics and environmental hazards, new conditions suspected of being linked to previous medical care or exposure to hazard, and long-term cohort studies.

It has always been accepted when explicit patient consent has not been obtained that the following questions should be answered. Why is explicit consent not possible? Why is it impractical? Does the study have a special scientific or public health imperative? Why is inclusion of those unable to give consent necessary? Is public safety an overriding concern? Attention to these questions has often been rather token and there has been an assumption that those in charge know best, but these are sometimes quite difficult questions to answer and their interpretation is variable. What is meant by public interest? What is required for high-quality research? Many of the issues relating to registration, surveillance and epidemiological research are complex. Some health professionals do not recognize the need for complete sets of patient data, arguing that (say) 80 or 90 per cent inclusion is adequate; yet the very people who are likely to be missing are the ones who may provide the most information within the data set of interest. The issues have been further complicated by recent national commitments and national programmes, such as those linked to cancer and heart disease, which set long-term targets. Again the evaluation of such programmes clearly demands high-quality data. Currently we are reaping the benefits of population cohort studies that were set up 20 years or more ago, some linked to mortality outcomes and some to subsequent generations. Can these data still be held and reanalysed many years after the initial consent? These studies were set up with different assumptions and codes of practice from those now being developed.

While the debate has concentrated on confidentiality, this must be seen in the wider context of the importance of information for health and healthcare. The UK has a proud tradition of high-quality information for health, with pioneering developments in record linkage and specific systems, such as the community health index in Scotland. The potential of these systems is still being developed and to destroy them now would be in no-one's interest. Indeed the continuation and development of such systems need not be at the cost of proper approaches to patient confidentiality.

Resolution

The current Health and Social Care Bill recognizes that, while full informed patient consent should be available wherever possible, there are some circumstances in which informed consent cannot or should not be obtained. The Bill will ensure that doctors can share patient information in circumstances in which stringent conditions are satisfied and if doing so will benefit the patient and the public. For example, it will allow us to maintain cancer registries, one of the best weapons against malignant disease[4].

The next stage should be an end to ill-informed and partial interpretation of existing legislation. The aim should be a consensus statement that avoids the current two-sided controversy. Everyone is in full agreement with the importance of patient consent and confidentiality. The Medical Research Council in the UK, in guidance to its funded researchers, has already published a comprehensive and clear document[5]. Among others, the Public Health Laboratory Service, the UK Association of Cancer Registries and the Heads of Academic Departments of Public Health have produced detailed and helpful documents relating to the various areas of surveillance, registers and research. However, good as they are, they lack authority. It is now necessary for the UK Departments of Health to produce a detailed discussion document during a transition period; this is a matter of urgency for clinicians and researchers. In the meantime nothing should be done that might destroy existing valuable data sets, reduce the surveillance of risks or produce incomplete registries.

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Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery

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Background: Anastomotic leak after gastrointestinal surgery is an important postoperative event that leads to significant morbidity and mortality. Postoperative leak rates are frequently used as an indicator of the quality of surgical care provided. Comparison of rates between and within institutions depends on the use of standard definitions and methods of measurement of anastomotic leak. The aim of this study was to review the definition and measurement of anastomotic leak after oesophagogastric, hepatopancreaticobiliary and lower gastrointestinal surgery.

Methods: A systematic review was undertaken of the published literature. Searches were carried out on five bibliographical databases (Medline, Embase, The Cochrane Library, Cumulative Index for Nursing and Allied Health Literature and HealthSTAR) for English language articles published between 1993 and 1999. Articles were critically appraised by two independent reviewers and data on definition and measurement of anastomotic leak were extracted.

Results: Ninety-seven studies were reviewed and a total of 56 separate definitions of anastomotic leak were identified at three sites: upper gastrointestinal (13 definitions), hepatopancreaticobiliary (14) and lower gastrointestinal (29). The majority of studies used a combination of clinical features and radiological investigations to define and detect anastomotic leak.

Conclusion: There is no universally accepted definition of anastomotic leak at any site. The definitions and values used to measure anastomotic failure vary extensively and preclude accurate comparison of rates between studies and institutions.

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Introduction

Leakage from an anastomosis in the gastrointestinal tract is a major complication that is often associated with increased morbidity, mortality and prolonged hospital stay. The frequency and consequences of anastomotic failure vary according to the site within the gastrointestinal tract. Anastomotic breakdown is the most important early complication after oesophageal anastomosis; incidences of up to 53 per cent have been reported[1]. It is also a serious complication after pancreatic surgery because dehiscence of anastomoses with autodigestion and destruction of surrounding tissue from leaking pancreatic juice is associated with a high mortality rate[2]. Dehiscence after colorectal anastomosis increases the perioperative mortality rate due to peritonitis and septicaemia, and adversely affects the late outcome in survivors because of increased local recurrence of carcinoma[3]. Anastomotic leak may be used as an indicator of the quality of surgical care, and comparisons of leak rates may be made between and within surgical centres[4]. However, the accuracy of such comparisons depends on the use of standard definitions and methods of measurement.

The aim of this study was to assess, systematically, the quality of definition, measurement, reporting and monitoring of anastomotic leak in the contemporary surgical literature. The study was undertaken within a wider systematic review of surgical adverse events.

Methods

Search strategy

A systematic search for English language literature published between 1993 and 1999 was undertaken on five biomedical bibliographical databases: Medline, Embase, Cumulative Index for Nursing and Allied Health Literature, The Cochrane Library and HealthSTAR. Initial searches focused on the validity and reliability of the definition and measurement of anastomotic leak. Owing to the lack of relevant literature, the search was subsequently expanded to include all prospective studies where anastomotic leak was included in the abstract, title or medical subject heading (MeSH). The final strategy consisted of textwords and MeSH terms on anastomosis (anastomosis, surgical; anastomotic leak, leakage, dehiscence, breakdown) combined with study design terms (prospective, longitudinal, follow-up, cohort studies).

Studies eligible for inclusion were those that contained a definition of anastomotic leak and/or details of clinical and radiological assessment. Articles were excluded for the following reasons: (1) retrospective study design; (2) failure to include a definition of anastomotic leak, a description of clinical features or methods used to detect leak; (3) non-gastrointestinal anastomoses; and (4) meta-analyses or review articles without inclusion of definitions, clinical features or investigations from primary studies. Reference lists from each study, review article and meta-analysis were searched for further relevant literature.

Critical appraisal and data extraction

The remit of the study was a systematic and comprehensive review of the definition, measurement and monitoring of anastomotic leak. Explicit criteria for evaluation and critical appraisal were determined at an early stage in the review and articles were appraised by two independent reviewers. The following data were extracted: study details; surgical procedure or intervention; definition of anastomotic leak; clinical factors considered in assessment; details of investigations undertaken; details on validity, accuracy, sensitivity, specificity, inter- and intra-rater reliability, practicality and acceptability of the definition, measure or diagnostic test.

Validity is an assessment of the extent to which something measures what it purports to measure. Definitions were assessed for face validity, or clinical sense, by noting what properties of leak were included. Reliability is an assessment of the extent to which the definition and measurement of anastomotic leak are repeatable and reproducible. If a definition has poor repeatability, this will lead to poor agreement between observers or different methods of measurement. Information was extracted on whether a definition or measurement was repeated on more than one occasion and/or by more than one observer, and estimates of repeatability (intra-rater reliability) and reproducibility (inter-rater reliability) were sought (e.g. κ values). Finally, definitions and methods of measurement must be acceptable, comprehensible and suitable for use in the clinical setting, and so comments on the practicality of definitions or methods were recorded.

Table 1 Anastomotic terminology

General anastomotic terms	Grading terms
Leak	Partial leak
Breakdown	Occult leak
Leakage	Complete leak
Insufficiency	Overt leak
Dehiscence	Minor, moderate, major leak
Competence	Covert leak
Suture insufficiency	Trivial clinical leak
Integrity	Gross leakage
Suture line disruption	Serious clinical leak
Security	Clinically silent leak
Frank clinical leak	Free leak
Patency	Subclinical leak
Controlled leak	Contained leak
Early leak	Asymptomatic leak
Radiological leak	Generalized leakage
Delayed or late leak	Symptomatic leak
Confirmed leak	Localized leakage
	Biochemical leak
	Clinical leak

Results

A total of 1908 abstracts were read and 240 articles were obtained for full critical appraisal. A large proportion of abstracts related to non-gastrointestinal anastomoses as a result of the sensitive rather than specific search strategy. Ninety-seven studies were included and the results are presented below according to broad location of surgery: upper gastrointestinal, hepatopancreaticobiliary (HPB) and lower gastrointestinal. *Table 1* illustrates the variation in terminology.

One 'standard' definition of anastomotic leak was proposed by the UK Surgical Infection Study Group (SISG) for use in clinical audit and to form the basis for meaningful comparisons[5]. Leak was defined as 'the leak of luminal contents from a surgical join between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicaemia, metabolic disturbance and/or multiple-organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localized area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a subclinical leak'. Although this definition was proposed in 1991, it has not been widely adopted; neither has it been used or referred to in any individual appraised study.

Upper gastrointestinal surgery

Thirty-three studies of oesophagogastric surgery were identified, only 13 of which included a definition of anastomotic leak or described the clinical features used to

Table 2 Overview of definition and assessment of upper gastrointestinal anastomotic leaks

Reference	Operation	Study design	Sample size	No. of leaks	Definition	Test	Timing of test*
Anikin *et al.*[6]	OG	Cohort	113	6 (5)	No	WS contrast	6
Choi *et al.*[7]	OG	RCT	40	0 (0)	Yes	WS contrast and endoscopy	7
Craig *et al.*[8]	OG	RCT	100	7 (7)	No	Barium contrast	5
Curry *et al.*[9]	RGB	Cohort	38	0 (0)	No	None routinely	—
Deshmane and Shinde[10]	OG	Cohort	75	5 (7)	Yes	Barium contrast	10
Fernandez-Fernandez *et al.*[11]	TG	Cohort	101	5 (5)	Yes	Unspecified contrast	7
Fernandez-Fernandez *et al.*[12]	TG	RCT	86	4 (5)	Yes	Unspecified contrast	7
Goel *et al.*[13]	OG	RCT	25	3 (12)	Yes	WS contrast	5
Gupta[14]	OG	Cohort	250	38 (15)	No	Unspecified contrast	5
Gupta *et al.*[15]	OG	Cohort	29	7 (24)	No	Unspecified contrast	NS
Hansson *et al.*[16]	OG	Cohort	53	14 (26)	No	WS contrast	7
Honkoop *et al.*[17]	OG	Cohort	269	60 (22)	No	WS contrast	7–10
Isozaki and Okajima[18]	G	Cohort	1114	52 (5)	Yes	WS contrast	7–14
Jacobi *et al.*[19]	OG	Cohort	33	6 (18)	No	WS contrast	7
Kuwano *et al.*[20]	OG	Cohort	69	5 (7)	Yes	WS contrast and Urografin infusion	14
Law *et al.*[21]	OG	RCT	122	4 (3)	No	WS contrast and endoscopy	7
Machens *et al.*[22]	OG	Cohort	12	6 (50)	Yes	WS contrast, drain amylase	7
Nambirajan *et al.*[23]	OA	Cohort	37	4 (11)	Yes	WS contrast	5–7
Obertop *et al.*[24]	OG	Cohort	10	7 (70)	Yes	Unspecified contrast and CT when suspected	—
O'Rourke *et al.*[25]	OG	Cohort	116	2 (2)	No	WS contrast	7–10
Pol *et al.*[26]	TG	Cohort	176	5 (3)	No	WS contrast	Week 2
Schardey *et al.*[27]	TG	RCT	205	14 (7)	Yes	WS contrast or indigo carmine blue test	7
Schilling *et al.*[28]	OG	Cohort	35	2 (6)	No	WS contrast	NS
Svanes *et al.*[29]	OG	Cohort	83	5 (6)	No	WS contrast	8–10
Swails *et al.*[30]	OG	RCT	25	3 (12)	No	WS contrast	4–5
Thiede *et al.*[31]†	OG	RCT	1042	6 (1)	Yes	WS contrast	8
Thomas *et al.*[32]	CI	Cohort	60	10 (17)	No	WS contrast	8–12
Trentino *et al.*[33]	OG	Cohort	39	4 (10)	No	WS contrast	8–9
van Lanschot *et al.*[34]	OG	RCT	60	14 (23)	No	WS contrast	7
Vigneswaran *et al.*[35]	OG	Cohort	131	32 (24)	No	WS contrast	7
Wu *et al.*[36]	G	Cohort	474	24 (5)	No	WS contrast	NS
Zieren *et al.*[37]	OG	RCT	107	20 (19)	Yes	WS contrast	7
Zilling *et al.*[38]	TG	Cohort	174	20 (11)	No	WS contrast	4–7

Definition or description of clinical assessment given in text. Values in parentheses are percentages. *Day or week after operation. †Upper and lower gastrointestinal procedures performed, but results for upper only presented here. WS, water-soluble; NS, not specified; OG, oesophagectomy or oesophagogastrectomy; G, gastrectomy; TG, total gastrectomy; OVA, oesophagovisceral anastomosis; RGB, resectional gastric bypass; OA, repair of oesophageal atresia; CI, colon interposition; RCT, randomized clinical trial; CT, computed tomography

judge anastomotic failure (*Table 2*). The clinical features used to assess upper gastrointestinal leak included: evidence of haematoma or seroma formation at the neck wound[7]; septicaemia[24]; peritonitis[18]; perianastomotic collection[10]; leak at the neck site[13]; local inflammation at anastomotic site or if air or saliva was found in the cervical drain bag[22]; and saliva in the chest drain, mediastinitis or abscess, pneumothorax, empyema[23].

Six studies relied on radiological extravasation of contrast medium[11,12,18,23,27,37]. The majority of studies reported routine postoperative use of radiographic water-soluble contrast swallows. Two groups of authors reported routine use of barium solution[8,10] and one group reported routine postoperative endoscopy with contrast studies[7]. The timing of administration of routine radiological tests ranged from 3 to 14 days after operation. Three studies conducted radiological investigation only when a leak was suspected clinically[9,24,39].

Five sets of authors proposed systems for classifying upper gastrointestinal leaks (*Table 2*). In general, an attempt was made to separate minor (detected radiologically) leaks from more major (clinically apparent) leaks[10,18,23]. Similarly, Csendes *et al.*[40] classified the radiological appearance of leakage as type I (localized) or type II (a great dissemination or diffusion to the pleural or abdominal cavities). These two types roughly correspond with the clinical and subclinical groups proposed by other authors. A meta-analysis by Bardini *et al.*[1] adds additional refinements to the above systems by defining four types of leak (*Table 3*). While the addition of a group including 'total disruption of the anastomosis resulting from an inadequate blood supply' is useful from the point of subsequent management, it

Table 3 Upper gastrointestinal classification systems

Reference	Grading	Description
Bardini *et al.*[1]	Radiological or minor	Asymptomatic and diagnosed only at radiographic check
	Clinical or moderate	Presence of fever, leucocytosis and local signs of inflammation
	Serious	Usually an early leak with severe disruption of the anastomosis
	Necrosis	Total disruption of the anastomosis resulting from an inadequate blood supply to the viscus sutured to the oesophagus and ischaemia of the area bordering the anastomosis
Csendes *et al.*[40]	Type 1 subclinical	A local fistula involving the anastomosis, with no spillage or dissemination through a fistulous tract to the pleural or abdominal cavity, or the appearance of contrast material in any abdominal drain
	Type II clinical	A leakage with great dissemination or diffusion to the pleural or abdominal cavity with the appearance of contrast medium in any of the abdominal drains
Deshmane and Shinde[10]	Small leak, asymptomatic	Detected only at radiological study
	Large leak, clinical	Perianastomotic collection manifested clinically
Isozaki and Okajima[18]	Minor	Leakage of contrast medium recognized radiologically as a fringe-like image from the anastomotic site or limited to a small area around the anastomotic site, but no leakage recognized from drain
	Major	Visualization of extensive intra-abdominal contrast medium radiologically and leakage of contrast medium from the drain, or cases where symptoms of peritonitis required the insertion of a new drain
Nambirajan *et al.*[23]	Incidental	Small radiological leak, no clinical symptoms
	Minor	Saliva in chest drain, but clinically well
	Major	Mediastinitis or abscess, pneumothorax, empyema, radiologically confirmed major oesophageal disruption

Table 4 Definition and assessment of hepatopancreaticobiliary anastomotic leaks

Reference	Operation	Study design	Sample size	No. of leaks	Definition*	Test
Bottger *et al.*[41]	P	Cohort	221	28 (13)	Yes	Amylase and drain fluid levels; relaparotomy
Chou *et al.*[42]	P	RCT	93	9 (10)	Yes	Amylase and drain fluid levels
Davidson *et al.*[43]	OLT	RCT	100	17 (17)	Yes	Routine retrograde cholangiography on day 10–14 after operation
Evans *et al.*[44]	P	Cohort	63	7 (11)	Yes	Amylase and drain fluid levels
Gupta *et al.*[45]	BDI	Cohort	13	3 (23)	Yes	Biliary nucleotide scintigraphy and transhepatic cholangiography (timing not stated)
Hamanaka and Suzuki[46]	P	Cohort	48	2 (4)	Yes	Routine Gastrografin swallow (day 7); amylase and drain fluid levels
Hardy *et al.*[47]	OLT	Cohort	129	7 (5)	Yes	Cholangiography or percutaneous transhepatic cholangiography (day 7)
Howard[48]	P	Cohort	56	0 (0)	Yes	Amylase and drain fluid levels
Kapoor *et al.*[49]	CJ	Cohort	41	6 (15)	No	Isotope hepatobiliary scanning (timing not stated)
Kayahara *et al.*[2]	P	Cohort	150	43 (29)	Yes	Drain fluid amylase content and radiological confirmation of pancreatic ductography (timing not stated)
Lowy *et al.*[50]	P	RCT	110	27 (25)	Yes	Amylase and drain fluid levels
Matsusue *et al.*[51]	P	Cohort	100	9 (9)	Yes	Amylase and drain fluid levels
Nagakawa *et al.*[52]	P	Cohort	64	10 (16)	Yes	Urinary and serum amylase levels
Reissman *et al.*[53]	P	Cohort	35	5 (14)	Yes	Amylase and drain fluid levels
Roder *et al.*[54]	P	Cohort	85	15 (18)	Yes	Radiologically documented leaks; amylase and drain fluid levels

Values in parentheses are percentages. *Definition or a description of investigation performed to detect leak. BDI, bile duct injury; CJ, cholangiojejunostomy; OLT, orthotopic liver transplantation; P, pancreatic surgery; RCT, randomized clinical trial

requires the use of endoscopy to verify an area of necrosis. Clearly, the more severe leaks have the least favourable outcome.

Hepatopancreaticobiliary surgery

Fifteen studies related to HPB surgery were eligible for inclusion: pancreatic surgery (11 studies), orthotopic liver transplant (two), cholangiojejunostomy (one) and bile duct injury (one). Fourteen of the 15 studies included a clear definition of HPB leak or described the investigations undertaken to detect leak (*Table 4*). The clinical signs extracted from individual studies included: peritonitis, pyrexia, sepsis[46]; bile drainage from drains placed at anastomosis area[45]; fever, raised leucocyte count, sepsis[54]. Kayahara *et al.*[2] accepted 'drainage of bile or enteric fluid

Table 5 Pancreatic surgery leak values

Reference	Description	Drain fluid volume	Amylase value	Timing
Bottger *et al.*[41]	Pancreatic fistula	—	Drain fluid amylase level > 2000 units/l	Daily
Chou *et al.*[42]	Pancreatic leak or fistula	Persistent drainage > 50 ml/day	Amylase-rich drain fluid	Daily for > 2 weeks
Evans *et al.*[44]	Pancreatic fistula	> 50 ml/day	Abdominal fluid level > 1000 units/l	Daily
Hamanaka and Suzuki[46]		Volume measured daily	—	Daily
Howard[48]	Pancreatic fistula	Peritoneal drain and pancreatic tube fluid assessed	Serum amylase level > 3 times normal; amylase levels in drain and tube fluid	2-day intervals for 8–12 days
Kayahara *et al.*[2]	Dehiscence	Drain removed when < 50 ml/day	Amylase in drain fluid > 3 times serum amylase level	Daily
Lowy *et al.*[50]	Clinical leak	Drain removed day 3 if < 200 ml/day and amylase level normal	> 2·5 times upper limit of normal in serum	Daily
	Biochemical leak	Drain fluid on or after day 3 that was asymptomatic and resolved spontaneously	> 2·5 times upper limit of normal for serum	Daily
Matsusue *et al.*[51]	Peripancreatic sepsis	Prolonged suppurative discharge < 50 ml/day	Low amylase drain fluid level < 1000 units for > 1 week	Daily
	Pancreatic fistula	Prolonged suppurative discharge > 50 ml/day	High amylase drain fluid level of > 1000 units for > 1 week	Daily
Nagakawa *et al.*[52]	Pancreatic leak	—	High urinary or serum amylase level for 3 days or more	Daily
Reissman *et al.*[53]	Pancreatic leak	Peripancreatic drain fluid for > 7 days	Amylase-rich fluid ≥ 40 ml/day (> 10 times normal plasma level)	Daily
Roder *et al.*[54]	Pancreatic fistula	Fluid collection of > 50 ml during entire postoperative course	Drain fluid amylase content > 3 times serum amylase level	

from the drain, the detection of enteric bacteria in the drainage fluid, radiographic confirmation of dehiscence of pancreatic ductography, or an amylase level in the drainage fluid of > 3 times the serum amylase level'. Each of the studies involving pancreatic surgery defined a leak by the volume of drain output and/or drain fluid enzyme concentrations (*Table 5*). There was considerable variation in fluid volume, values and the timing of test administration between individual studies.

Two HPB classification systems were identified[50,51]. Matsusue *et al.*[51] distinguished between peripancreatic sepsis and a pancreatic fistula, based on amylase content and level of drainage fluid in patients undergoing pancreaticojejunostomy. In a randomized controlled trial of octreotide after pancreaticoduodenectomy, Lowy *et al.*[50] gave clear criteria for clinical and biochemical pancreatic leaks. A clinical pancreatic anastomotic leak was defined as the drainage of amylase-rich fluid (more than 2·5 times the upper limit of normal for serum amylase) in association with fever (above 38°C), leucocytosis (white blood cell count greater than 10 000 per litre), sepsis (haemodynamic instability requiring transfer to the intensive care unit) or the need for percutaneous drainage of an amylase-rich fluid collection. A biochemical pancreatic leak was defined as a raised level of amylase (more than 2·5 times the upper limit of normal for serum amylase) in the drain fluid on or after postoperative day 3 that was asymptomatic and resolved spontaneously. This was the only study with distinct parameters for sepsis, leucocytosis and fever.

One review was identified that examined the efficacy of octreotide, a potent inhibitor of exocrine pancreatic secretion, in reducing postoperative complications[55]. The authors distinguished between pancreatic leakage and pancreatic fistula, where leakage was defined as 'leakage from pancreatic, biliary, or intestinal anastomosis as determined by radiographic or intraoperative findings/relaparotomy'. A pancreatic fistula was diagnosed 'if (1) the concentrations of amylase and lipase in the drainage fluid were > 3 times higher than in the serum of *n* [not specified by authors] consecutive postoperative days and (2) a drainage volume of > 10 ml/24 h was present. The serum and drainage fluid amylase and/or lipase concentration were determined on postoperative days 1, 3, 4, 5 and 7 and twice weekly thereafter'. However, only two of the original seven controlled trials had used these standard definitions.

Lower gastrointestinal surgery

A total of 49 lower gastrointestinal studies were eligible for inclusion, 29 of which included a definition (*Table 6*). The clinical signs and symptoms most frequently described included: signs of localized or generalized peritonitis (12 studies); faecal discharge from the wound and/or drain (11);

Table 6 Definition and assessment of lower gastrointestinal anastomotic leaks

Reference	Operation	Study design	Sample size	No. of leaks	Definition	Test	Timing
Ambrosetti *et al.*[56]	CR	Cohort	199	5 (3)	No	WS contrast	Routine on day 9–11
Biondo *et al.*[57]	CR	Cohort	63	3 (5)	No	Unspecified contrast	When suspected
Bokey *et al.*[58]	C/CR	Cohort	1846	79 (4)	Yes	WS contrast, abdominal reoperation	When suspected
Bouillot *et al.*[59]	C	Cohort	50	1 (2)	No	Unspecified radiography	Unclear
Burke *et al.*[60]	CR	RCT	186	7 (4)	Yes	WS contrast	Routinely on day 7 in first half of study, then changed to when leak suspected
Cornwell *et al.*[61]	C	Cohort	56	3 (5)	Yes	Surgical re-exploration, CT or WS contrast	Variable
De Wever *et al.*[62]	CR	Cohort	16	5 (31)	No	Endoscopy and unspecified radiological test	3–4 months
Debus *et al.*[63]	CR	Cohort	77	6 (8)	No	Barium contrast	When suspected
Deen and Smart[64]	C	Cohort	53	2 (4)	Yes	Unspecified radiography	When suspected
Dehni *et al.*[65]	CR	Cohort	258	31 (12)	Yes	WS contrast, imaging or reoperation	Routine contrast study 8–10 weeks before stoma
Docherty *et al.*[66]	CR	RCT	652	38 (6)	Yes	WS contrast, reoperation	Routine on day 4–14
Fingerhut *et al.*[67]	CR	RCT	159	10 (6)	Yes	WS contrast, sinography	Routine contrast study on day 7
Fingerhut *et al.*[68]	CR	RCT	113	17 (15)	Yes	WS contrast, sinography, reoperation	Routine contrast study on day 7
Hallbook *et al.*[69]	CR	RCT	97	9 (9)	Yes	Digital and endoscopic examination, contrast, reoperation, CT	Routine contrast study before stoma closure
Hansen *et al.*[70]	CR	Cohort	615	9 (1)	Yes	Unspecified radiography	When suspected
Hida *et al.*[71]	CR	RCT	43	2 (5)	No	WS contrast	Routinely at 2 months
Iversen *et al.*[72]	CR	Cohort	161	17 (11)	No	WS contrast	When suspected
Junger *et al.*[73]					Yes	LPS concentration	LPS level assessed daily
Karanjia *et al.*[74]	CR	Cohort	219	38 (17)	Yes	WS contrast	When suspected
Kessler *et al.*[75]	CR	MRCT	621	88 (14)	Yes	Unspecified radiological tests, methylene blue test	When suspected
Kockerling *et al.*[76]	CR	MRCT	949	46 (5)	No	Unspecified	Unspecified
Kracht *et al.*[77]	C	MRCT	440	31 (7)	Yes	WS contrast, reoperation	Routine contrast on day 8–10
Mann *et al.*[78]	CR	Cohort	370	11 (3)	Yes	WS contrast	When suspected
Merad *et al.*[79]	CR	RCT	705	53 (8)	Yes	WS contrast, reoperation	Routine contrast on day 8
Merad *et al.*[80]	CR	RCT	494	32 (6)	Yes	WS contrast, reoperation	Routine contrast on day 7
Miller *et al.*[81,82]	CR	Cohort	103	6 (6)	Yes	WS contrast	Routine contrast on day 10
Moore *et al.*[83]	CR	Cohort	300	34 (11)	No	Unspecified radiological examination, reoperation (clinically significant)	Routine before stoma closure
Norris *et al.*[84]	L	Cohort	156	6 (4)	No	Unspecified imaging or reoperation	When suspected
Pakkastie *et al.*[85]	CR	RCT	38	15 (39)	Yes	WS contrast	Routine contrast on day 7–10
Petersen *et al.*[3]	CR	Cohort	467	41 (9)	Yes	WS contrast	When suspected
Redmond *et al.*[86]	CR	Cohort	111	13 (12)	Yes	WS contrast	Routine contrast on day 10–12
Sagar *et al.*[87]	CR	RCT	100	12 (12)	Yes	WS contrast	Routine contrast on day 5–7
Santos *et al.*[88]	CR	RCT	149	11 (7)	Yes	Unspecified radiological examination	When suspected
Slim *et al.*[89]	Lap CR	Cohort	65	6 (9)	Yes	WS contrast, reoperation for peritonitis	When suspected
Stewart *et al.*[90]	CR	RCT	88	1 (1)	Yes	Unspecified	Unspecified
Tagart[91]	CR	Cohort	220	79 (36)	No	Limited barium contrast	Routine contrast on day 14
Thompson *et al.*[4]	CR	Cohort	535	18 (3)	No	None	Unspecified (not done routinely)
Watson *et al.*[92]	C/CR	Cohort	477	9 (2)	No	WS contrast	When suspected
Wheeler and Gilbert[93]	CR	Cohort	102	7 (7)	No	WS contrast	Routine contrast on day 8

Values in parentheses are percentages. C, colonic resection; CR, colorectal surgery; CT, computed tomography; L, laparotomy (for Crohn's disease); Lap, laparoscopic; LPS, lipopolysaccharide; MRCT, multi-randomized clinical trial; RCT, randomized clinical trial; WS, water-soluble

abscess (ten); purulent discharge from drain, wound or anus (seven); and fever (six). Some studies defined a clinical anastomotic leak as that requiring reoperation[83,86], whereas others accepted signs of leakage without further surgery. None of the studies defined peritonitis.

The majority of lower gastrointestinal series used contrast (water-soluble) radiography, either routinely or when a leak was suspected. Assessment of timing of administration was often difficult to interpret as some authors combined leak results from routine investigation with those conducted when leak was suspected. The timing of administration of routine contrast ranged from day 4 to day 14 after operation, although timing was later in patients with an ileoanal pouch (*Table* 7).

Table 7 Definition and assessment of ileoanal pouch leaks

Reference	Operation	Study design	Sample size	No. of leaks	Definition	Test	Timing
Breen *et al.*[94]	IPAA	Cohort	628	28 (4)	Yes	WS contrast	Routinely before stoma closure
Dayton and Larsen[95]	IPAA	Cohort	510	21 (4)	Yes	—	Unclear
Flohr *et al.*[96]	Ileal neobladder	Cohort	306	1 (0)	No	Multiple investigations performed (ileal neobladder); IVP and voiding cystography at 1 year	Routine IVP and cystography at 1 year
Hrung *et al.*[97]	IPAA	Cohort	37	3 (8)	Yes	WS and/or barium contrast	Routine imaging at 8–12 weeks
Hulten[98]	IPAA	Cohort	307	31 (10)	Yes	Endoscopy and radiological examination	Routine contrast 6–8 weeks before closure of ileostomy or when suspected
Kartheuser *et al.*[99]	IPAA	Cohort	171	2 (1)	No	Unspecified radiological investigation under general anaesthesia	2 months
Kelly *et al.*[100]	IPAA	Cohort	85	10 (12)	Yes	Unspecified contrast	5–6 weeks before stoma closure
Richard *et al.*[101]	Pelvic pouch	Cohort	753	91 (12)	No	WS contrast or CT with contrast	Unspecified
Wexner *et al.*[102]	IAA	Cohort	83	0 (0)	No	Unspecified contrast	Routine contrast before stoma closure, time not specified

Values in parentheses are percentages. CT, computed tomography; IAA, ileoanal anastomosis; IPAA, ileal pouch–anal anastomosis; IVP, intravenous pyelography; WS, water-soluble

Discussion

This review identified a total of 56 definitions of anastomotic leak from 97 studies but failed to identify any formal validity evaluation of the identified definitions and classifications. Although a standard definition for anastomotic leak was proposed by a UK multidisciplinary group (SISG)[5], this definition was not used or referred to by any of the appraised studies, perhaps because it is too general for use in different clinical situations. Other studies have developed definitions and grading systems specific to parts of the gastrointestinal tract and so studies were subdivided in the review by the location of surgery.

In the 33 papers reviewed that involved oesophagogastric surgery, the grading systems for leakage contained components similar to those in the SISG definition: fever, abscess and organ failure. Most authors reported using routine water-soluble contrast investigation in the first postoperative week. Rates of postoperative leaks may be influenced according to timing of administration and standard procedures and/or protocols. The postoperative leak rates for 31 upper gastrointestinal studies (excluding two containing fewer than 12 patients[22,24]) ranged from 0 to 26 per cent. Although Curry *et al.*[9] reported no postoperative leaks, routine postoperative radiography was not performed and asymptomatic leaks could not have been detected.

Following biliary and pancreatic anastomoses, leakage of bile and pancreatic fluid is common but not clinically relevant if there are no untoward clinical symptoms. Such leakage in the first few days after operation ceases spontaneously. Excess and/or prolonged drainage of fluid has been used in HPB studies. However, the values for drainage volume and enzyme concentration required to diagnose clinically significant leakage varied considerably between centres. For example, drain fluid amylase levels ranged from 2·5 to 10 times normal plasma levels. In studies of pancreatic surgery, leak rates ranged from 0 to 29 per cent. Furthermore, the arbitrary levels of drainage volume and amylase content used by some authors will be greatly influenced by the use of octreotide, which effectively eliminates pancreatic exocrine function, and the concentration of enzymes in drain fluid.

There were more clinical trials and larger sample sizes in the studies of lower gastrointestinal surgery. The German Colorectal Carcinoma Study Group reported leak rates in a large cohort based on clinical assessment of leak without radiological confirmation[75]. Results were presented according to individual criteria for faecal fistula, local abscess and peritonitis, with overall anastomotic leak rates. The presentation of individual features of clinical leakage permits intra- and inter-institutional comparison. While the rate of leakage increases with lower anastomoses, and this may make direct examination easier, the level of a colorectal anastomosis does not influence the definition or diagnosis of a leak. Overall, clinical features were used more commonly for diagnosis in the lower gastrointestinal studies than in studies of upper gastrointestinal and HPB surgery. The definitions of leak after bowel surgery usually included peritonitis (localized or generalized), faecal or purulent drainage from the wound and/or drain, presence of an abscess, and fever. Fifteen lower gastrointestinal reports in this review described routine contrast examination during the first or second postoperative week to determine

Table 8 Components of definition of anastomotic leak by anatomical site

Grade	Symptoms and signs	Management
Upper GI leak		
Radiological	Detected only on routine imaging; no clinical signs	No change in management
Clinical minor	Presence of luminal contents through the drain or wound site causing local inflammation, e.g. fever (temperature > 38°C) or leucocytosis (white cell count > 10 000/litre). Leak may also be detected on imaging studies	No change in management or intervention but may have prolonged hospital stay and/or delay in resuming oral intake
Clinical major	As clinical minor. Severe disruption to anastomosis. Leak may also be detected on imaging studies	Change in management and intervention required
HPB leak		
Radiological	Detected only on routine imaging study. No clinical signs	No change in immediate management
Clinical minor	Leakage defined if persistent drainage of > 50 ml per day via drain or serum amylase level > 2 times normal or signs of fever (temperature > 38°C) or leucocytosis (white cell count > 10 000/litre). Leak may also be detected on imaging studies	No change in management or intervention. May have prolonged hospital stay
Clinical major	As clinical minor. Severe disruption to anastomosis. Leak may also be detected on imaging studies	Change in management and intervention required
Lower GI leak		
Radiological	Detected only on routine study. No clinical signs	No change in management
Clinical minor	Presence of luminal contents through the drain or wound site causing local inflammation, e.g. fever (temperature > 38°C), leucocytosis (white cell count > 10 000/litre), faecal discharge from wound or drain or abscess. Leak may also be detected on imaging studies	No change in management or intervention but may have prolonged hospital stay
Clinical major	As clinical minor. Severe disruption to anastomosis. Leak may also be detected on imaging studies	Change in management and intervention required

GI, gastrointestinal; HPB, hepatopancreaticobiliary

anastomotic integrity. Such tests are no longer routine in most practices because of the clinical irrelevance of occult leaks and the small risk of radiological investigation[60].

The Australian Council of Healthcare Standards accepted anastomotic leak as a clinical outcome indicator for colorectal carcinoma resection on the basis that clinical leaks are 'easily identifiable'[103]. However, clear, well defined criteria must be agreed on to ensure that postoperative leak prevalence rates are directly comparable. At present, there is considerable variation in the definition and interpretation of clinical leakage and, until single definitions are adopted, it is unlikely that inter-institutional comparisons are valid. Validity assessment is hampered by the lack of a standard definition that has been accepted by surgeons. The majority of the definitions require subjective assessment, particularly the definitions in lower bowel surgery, which tend to depend on clinical judgement. These definitions will be subject to variation in interpretation, as clinical assessment is likely to be made by more than one member of a surgical team over a period of hospital stay. Assessment and diagnosis of anastomotic leak may differ between surgeons according to grade and experience. No formal assessment of inter-rater reliability was found in this review. The application of a single definition of anastomotic leak by two independent assessors to the same group of patients would allow assessment of reproducibility (inter-rater reliability). Statistical estimates of agreement between assessors using definitions of other postoperative surgical events (e.g. wound infection, deep vein thrombosis) have been conducted, but this systematic review failed to find evidence of similar work for anastomotic leak.

There was no chronological element in the definitions of anastomotic leakage, as is routine for postoperative mortality (30-day cut-off) or late wound infection detected after discharge from hospital (30 days). This criterion should be considered for inclusion in the definition of anastomotic leakage because such leakage may become apparent only after discharge from hospital. Readmission may be required because of sepsis or fistula formation but occasionally leakage that was clinically occult may be demonstrated on routine contrast radiology performed, for example, before closure of a stoma. It seems logical to categorize leaks according to timing of presentation. A number of patients will die after an operation that included an intestinal anastomosis, but not all will have had anastomotic integrity confirmed before death by contrast radiology. In some of these patients an autopsy will reveal occult leakage or confirm suspected leakage. The post-mortem examination rate for patients who die after anastomotic surgery should be stated in all reports.

The SISG definition of anastomotic leak is useful as a generic definition. *Table 8* shows a proposal for three definitions specific to anatomical site, based on components from the SISG definition and those identified in the systematic review. These definitions include signs and symptoms, level of severity, and components of clinical management. In essence, any leak that requires a change in management, including prescription of antibiotics, with subsequent delay in the reintroduction of oral intake or discharge from hospital, would be considered a major clinical leak. The definitions proposed in this review may stimulate debate. Acceptance of a standard definition among surgeons is an important step for clinical audit and epidemiological research.

Conclusion

No validated definition of anastomotic leak by site was found in the contemporary literature. One definition of anastomotic leak was proposed at a UK consensus workshop, but no evidence was found for its use other than in the original publication. There is a need for surgeons to agree a standard definition by anatomical site, that is valid and reliable. It should distinguish between clinically minor (radiological) and major anastomotic leaks after gastrointestinal surgery.

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Penetrating atherosclerotic ulcers of the aorta

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Background: Penetrating aortic ulcers burrow into the aortic wall and can have fatal consequences. Although they were first described as long ago as 1934 they have only recently been recognized as a distinct pathological entity.

Method: A review of the current literature was undertaken, based primarily on an English language Medline search with secondary references obtained from key articles.

Results: Penetrating aortic ulcer is principally a disease of elderly hypertensive men. It may run a benign course or may produce complications such as aortic rupture, embolization and aneurysm formation. Presentation may be identical to that of classical aortic dissection, but the distinction is important because an ulcer may be more likely to cause rupture.

Conclusion: Open surgical repair has been the 'gold standard' of treatment but endovascular stenting is an attractive option in this group of frail patients.

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Introduction

Atherosclerosis is arguably the prime disorder leading to morbidity and death in the Western world. A prominent feature of advanced atherosclerotic plaque is superficial ulceration, usually limited to the intima[1,2]. Shennan[3] was first to describe penetrating atherosclerotic ulceration of the thoracic aorta in 1934 and his observations were enhanced by Stanson *et al.*[4] in 1986. They described a progression of the atherosclerotic process in which the ulcer penetrates through the internal elastic lamina and extends into the media. Progression of penetration can result in death[4]. This article attempts to review the current literature on this interesting condition and highlights the development of new methods of treatment. It is based on an English language Medline search from January 1966 to March 2001; secondary references were also obtained from the reference sections of key papers.

Pathology

The true incidences of both symptomatic and silent penetrating atherosclerotic ulcer are not known as no appropriately designed studies have been carried out to answer this question. However, some indication of its incidence compared with that of other aortic emergencies may be drawn from a series of 194 consecutive patients examined by transoesophageal echocardiography (TOE) to investigate aortic disease[5]. There were 12 cases of ulcer, 93 of intramural haematoma or classical dissection, 18 of aneurysm and four of coarctation; 97 studies were normal. Coady *et al.*[6] retrospectively reviewed the images of 198 patients initially diagnosed with aortic dissection and concluded that 15 had actually had a penetrating atherosclerotic ulcer.

Penetrating aortic ulcer is a condition of elderly hypertensive men (*Table 1*). There may be one or more ulcers ranging in diameter from 5 to 25 mm and in depth from 4 to 30 mm[14]. Ulceration has been described along the whole length of the aorta but the most common sites are the mid and distal descending thoracic segments. It may occur in an aorta of normal calibre but is more often found in aortas of increased diameter[6,8,9]. Ulcers have also been described in the walls of both thoracic and abdominal aortic aneurysms[5,6,15], and a strong association exists between these ulcers and concomitant or previously treated aneurysm(s) at other sites[9]. The commonest site for such aneurysm development is the abdominal aorta but other locations include the iliac, popliteal and splenic arteries (*Table 1*).

Histological examination usually shows extensive surrounding atherosclerosis with the ulcer penetrating the

Table 1 Features of penetrating aortic ulcer

Reference	Year	No. of patients	Mean age (years)	Hypertensive	Site of ulcer	Presence of aneurysm	Chest and/or back pain on presentation
Stanson *et al.*[4]	1986	8M, 8F	73	13	8 distal third of thoracic aorta 7 middle third of thoracic aorta 5 proximal third of thoracic aorta 1 ascending thoracic aorta	12 unassociated, concomitant aneurysm	13
Yucel *et al.*[7]	1990	5M, 2F	70	n.s.	Thoracic aorta	n.s.	7
Kazerooni *et al.*[8]	1992	7M, 9F	74	14	14 middle/distal third of thoracic aorta 2 proximal third of thoracic aorta NB 1 had multiple ulcers including the aortic arch and suprarenal aorta	3 abdominal aorta 1 ascending thoracic aorta 1 descending thoracic aorta 1 thoracoabdominal	13
Harris *et al.*[9]	1994	10M, 8F	74	14	29 ulcers in 18 patients: 9 distal third of thoracic aorta 7 infrarenal abdominal aorta 5 middle third of thoracic aorta 4 proximal third of thoracic aorta 3 suprarenal abdominal aorta 1 aortic arch	12 had 17 concomitant aneurysms 9 were associated with the ulcer: 4 distal third of thoracic aorta 2 proximal third of thoracic aorta 1 middle third of thoracic aorta 1 aortic arch 5 infrarenal abdominal aorta 2 popliteal artery 1 iliac artery 1 splenic artery	4
Coady *et al.*[6]	1998	9M, 6F	77	15	13 descending thoracic aorta 2 ascending thoracic aorta	6 had previous diagnosed or managed abdominal aortic aneurysm	12
Vilacosta *et al.*[5]	1998	12M, 0F	65	12	8 descending thoracic aorta 2 ascending thoracic aorta 2 aortic arch	2 had ulcer in aneurysm: 1 descending thoracic aorta 1 aortic arch	12
Brittenden *et al.*[10]	1999	2M, 0F	72	0	2 middle third of thoracic aorta	1 previous abdominal aortic aneurysm repair	2
Murgo *et al.*[11]	1998	3M, 1F	76	4	Mid and distal descending thoracic aorta	n.s.	4
Hayashi *et al.*[12]	2000	11M, 1F	72	n.s.	6 proximal descending thoracic aorta 5 distal descending thoracic aorta 1 abdominal aorta	4 abdominal aorta 2 thoracoabdominal	n.s.
Quint *et al.*[13]	2001	20M, 18F	72	n.s.	56 ulcers in 38 patients: 1 ascending thoracic aorta 14 aortic arch 15 proximal descending thoracic aorta 20 distal descending thoracic aorta 6 abdominal aorta	n.s.	21

M, male; F, female; n.s., not stated

internal elastic lamina and extending into the media[2,12]. The media is thus exposed to pulsatile blood flow, resulting in an intramural haematoma and a variable degree of aortic dissection. Once formed, the ulcer may remain quiescent or the pathological process may progress, with several potential complications. The ulceration may weaken the aortic wall resulting in aneurysm formation, or the inflammation and/or limited dissection surrounding an ulcer in the ascending aorta may disrupt the aortic valve resulting in regurgitation[9,16,17]. More dramatically, the ulcer may penetrate the full thickness of the media resulting in a pseudoaneurysm, fistulation into adjacent organs (such as the oesophagus or bronchus), or even free rupture[2,6,8,12,18,19].

Classical aortic dissection, intramural haematoma and penetrating ulceration

Classical aortic dissection, intramural haematoma and penetrating ulceration are three potentially fatal aortic diseases that may be indistinguishable clinically. The risk factors associated with classical dissection include inherited disorders of connective tissue (e.g. Marfan's syndrome), hypertension, aneurysm, bicuspid aortic valve, vasa vasorum rupture and pregnancy[6,20,21]. In such dissection a laceration of the intima and inner layer of media allows blood to dissect along the outer part of the media, resulting in a smooth intimal flap that extends across the aorta to create a false channel that encroaches on the true lumen[20].

The length of aorta involved in the dissection is often extensive[22]. Debate continues about whether atherosclerosis itself can lead to dissection; most authorities now believe it does not[20]. Although there are reports of dissection arising from an atheromatous ulcer, they account for only a small proportion of cases of dissection and, in addition, aortic dissection occurs most often in the ascending aorta, where atherosclerosis is less commonly encountered[3]. In contrast, a penetrating ulcer is invariably surrounded by extensive atherosclerosis and is most often found in the mid and distal thoracic aorta. In company with the ulcer there may be an area of aortic dissection with or without an associated intimal flap. However, this differs from classical dissection because the flap, if present, is irregular and thick, the dissection does not usually encroach on the aortic lumen, and it is usually of limited length[23]. The reason for the limited length of dissection may be that the plane of dissection is lost owing to scarring or atrophy of the media secondary to the atherosclerotic process[22]. The third condition, intramural haematoma, is a concentrically located collection of blood within the media of the aortic wall, without evidence of intimal disruption or penetrating ulcer. Like penetrating ulcer, it is most often found in the descending thoracic aorta[24,25]. It may be the result of haemorrhage from the aortic vasa vasorum or rupture of an atherosclerotic plaque[26]. While these three conditions are pathologically distinct, distinguishing between them clinically may be difficult or even impossible in some cases[12]. Still, it is important to make an exact diagnosis because the risk of rupture may be significantly higher in patients with an ulcer or intramural haematoma than in those with classical dissection[20]. *Table 2* summarizes various characteristics that distinguish penetrating ulcer, intramural haematoma and aortic dissection.

Clinical features of penetrating ulcer

Sudden-onset severe chest and/or back pain in an elderly hypertensive patient may suggest an imminent cardiovascular catastrophe[2]. The differential diagnosis in this situation includes acute coronary syndromes, aortic dissection, intramural haematoma, true aneurysm and pulmonary embolism, as well as penetrating ulcer of the aorta[25]. Most patients present acutely in this way, presumably as a result of the local effects of the ulcer (*Table 1*). Anterior pain tends to correlate with ascending aortic lesions while descending aortic lesions usually cause back pain[20]. With penetrating ulcer there is a paucity of specific clinical signs; in particular, there is no pulse deficit, aortic regurgitation, stroke or visceral vessel compromise[2]. The presence of any of these suggests a classical dissection. Nevertheless, there have been two reported cases of a penetrating ulcer associated with aortic valve regurgitation[16,17]. A pleural effusion should not distract the clinician from a diagnosis of an ulcer since this was present in seven of 16 cases in one series; it may be serous or haemorrhagic[8]. A less common presentation is embolization of atheromatous debris or an overlying thrombus, resulting in ischaemia and even infarction of downstream tissues. Documented examples of this are cerebral vascular accident and distal lower-limb

Table 2 Characteristics distinguishing penetrating aortic ulcer, intramural haematoma and aortic dissection

	Penetrating ulcer	Intramural haematoma	Aortic dissection
Patient profile	Elderly; hypertensive	Elderly; hypertensive	Generally younger; hypertensive
Symptoms	Severe chest and/or back pain	Severe chest and/or back pain	Severe chest and/or back pain
Signs	Usually absent; occasional aortic valve insufficiency	Usually absent; occasional aortic valve insufficiency	Pulse inequality; compromise of flow in visceral vessels; neurological deficits; aortic valve insufficiency
Location	Largely descending	Largely descending	Ascending and descending
Extent of lesion	Focal	Focal	Usually extensive
Degree of atherosclerosis	Always severe	Variable	Variable (often minimal)
Aortic size	Largest: approx. 6·2 cm	Larger: approx. 5·5 cm	Smaller: approx. 5·2 cm
Concomitant abbdominal aortic aneurysm	Common	Common	Occasional
Diagnostic studies	Localized ulceration into the aortic wall; intramural haematoma; displacement of intimal calcification; no false lumen visible	Haematoma within aortic wall; no intimal flap; no ulcer crater	Intimal flap with displacement of intimal calcification with contrast medium within false lumen

Modified from Coady *et al.*[20] and Cooke *et al.*[2]

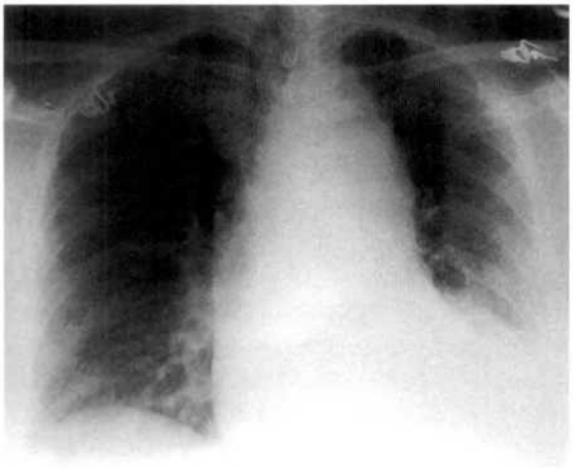

Fig. 1 Chest radiograph of a patient with a penetrating ulcer in the proximal descending thoracic aorta. Note the widened mediastinum, deviated trachea and left pleural effusion

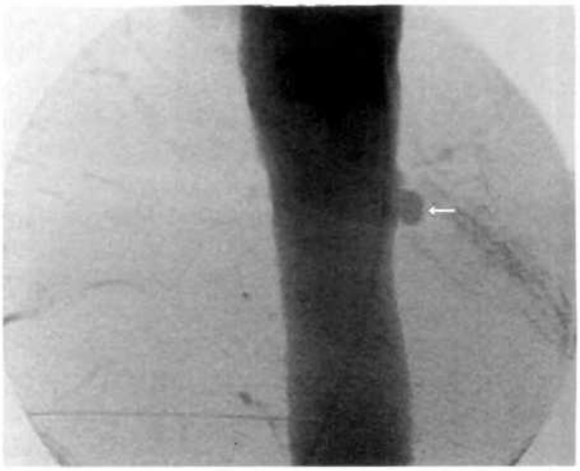

Fig. 2 Angiogram of patient in *Fig. 1*. Note the filling of the crater-like ulcer

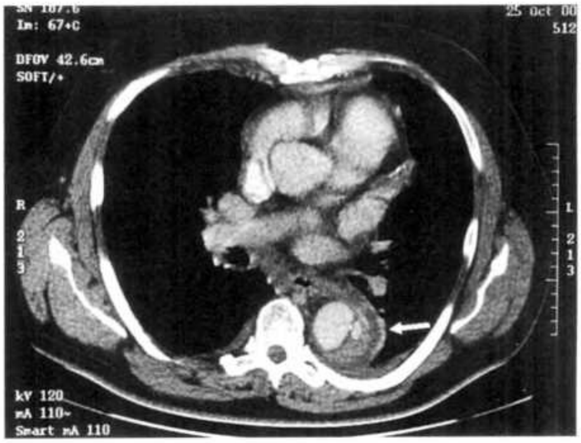

Fig. 3 Computed tomogram of patient in *Figs 1* and *2*. Note the thickened aortic wall and inward displacement of the calcified intima by intramural haematoma

ischaemia[9,10]. Rarely, the mediastinal haematoma from a perforated aorta may cause specific symptoms such as upper airway and oesophageal obstruction[27]. It should also be remembered that an asymptomatic penetrating ulcer may be detected incidentally during radiological imaging for an unrelated condition[9].

Imaging

A clue to the diagnosis of an ulcer can often be gleaned from the chest radiograph (*Fig. 1*); this investigation was abnormal in all 16 cases in one series[8] . Plain radiographic findings include a widened mediastinum, diffuse enlargement of the descending thoracic aorta, pleural effusion, a left apical mass and a deviated trachea[8,28]. However, to obtain a precise diagnosis further imaging is required, such as angiography, computed tomography (CT), magnetic resonance imaging (MRI) or TOE (*Figs 2* and *3*)[7,23,29,30].

Angiography has become less popular as a first-line investigation because of its invasive nature and because it may give rise to false-negative results if the ulcer is not profiled on the projections obtained[30]. The appearance on CT, MRI or TOE is of a crater-like outpouching of the lumen, with a thickened aortic wall and inward displacement of the calcified intima by the intramural haematoma[5,7,31]. There is usually evidence of severe atherosclerosis of the surrounding aorta. Imaging may also reveal pleural and pericardial fluid, mediastinal haematoma or a pseudoaneurysm. There is evidence that the presence of a pleural effusion is a risk factor for progression of the ulceration[13]. Penetrating ulceration may be more difficult to identify by TOE than by CT or MRI; MRI may be best at differentiating intramural haematoma from atherosclerotic plaque and chronic intraluminal thrombus[32,33].

Natural history

Stanson *et al.*[4] reviewed the results of 684 aortograms and found that 16 met the criteria for penetrating ulcer. In 13 of these 16 cases presentation was with chest and/or back pain. Seven of the 16 patients were treated conservatively but developed recurrent symptoms prompting surgical intervention. Overall, operative repair was carried out in 14 of the 16 patients and in seven of these a contained rupture was identified.

A high incidence of complications associated with ulceration was documented in the series of 15 patients reported by Coady *et al.*[6]. These patients were identified by a review of records and imaging of 198 patients with an initial diagnosis of aortic dissection. Of note is that 12 of 15 presented with chest and/or back pain. Operative repair was carried out in four of the 15 and the other 11 patients were managed medically. Of these 11, the aorta ruptured in three during treatment and eight were discharged from hospital pain free. Overall, rupture occurred in six (40 per cent) of 15 patients with an ulcer during the observation period compared with six (7 per cent) of 82 patients with type A dissection and four (4 per cent) of 101 patients with type B dissection.

In contrast, Harris *et al.*[9] reported a series of 18 patients with a total of 29 penetrating ulcers between them. Of note is that only four of these 18 patients presented with chest and/or back pain while two presented with distal embolization and one presented with a contained rupture after receiving intravenous heparin for deep venous thrombosis. The remaining 11 patients had the ulceration detected incidentally. Long-term follow-up, from 1 to 7 years, was available in ten patients with 17 ulcers (including the four patients who presented with pain). The pain settled in half those affected but the remaining pair had recurrent pain; one had enlargement of the aorta at an ulcer site and the other had developed a 7·8-cm saccular thoracic aneurysm after 6 years. Overall, of the 17 ulcers with long-term follow-up, there was a progression to saccular aneurysm in four, fusiform aneurysm in one, and one patient developed a complex saccular/fusiform aneurysm. Progression to saccular aneurysm occurred in all cases once focal periaortic adventitial bulging was observed, with an average growth rate of 0·31 cm (or 7·2 per cent) per year. Two ulcers were associated with an increased aortic diameter and nine remained unchanged. Interestingly, in the patient who developed a fusiform aneurysm and in those who had a subaneurysmal increase in aortic diameter, the ulcer crater reduced in definition or disappeared, suggesting that it had become incorporated into the aortic wall.

Quint *et al.*[13] published a series of 38 patients with 56 ulcers of whom 21 presented with chest and/or back pain. Long-term follow-up with repeated CT was available for 33 ulcers over 2–78 months. Over this time 21 of the 33 lesions were stable, two regressed and ten progressed. Progression was defined as an increase in the size of the aorta, the ulcer or both. Surgical intervention was required for eight ulcers, because they were either symptomatic (two) or had an associated aneurysm (six).

Kazerooni *et al.*[8] described a series of 16 patients of whom five had been reported previously[34]; 13 of the 16 had back and/or chest pain on presentation and in the remaining three the lesion was an incidental finding. Seven patients underwent surgical intervention because of cardiovascular instability, continued haemorrhage, persisting pain or a contained perforation/pseudoaneurysm. Nine received medical therapy during which the pain resolved, allowing discharge home in eight cases. The last of these nine patients was deemed an excessive surgical risk and underwent successful coil embolization of the ulcer and associated pseudoaneurysm[28]. Four of the eight patients who were treated medically were followed for a median of 17 weeks. The previously documented ulcer had become incorporated into the aortic wall, which was enlarged in three patients. One medically managed patient developed a focal perforation/pseudoaneurysm during follow-up.

Hayashi *et al.*[12] reported a series of 12 patients with penetrating ulcer. Four patients underwent surgical intervention for recurrent pain or enlargement of the ulcer and two died as a result of rupture. Interestingly, the other six patients were followed for between 21 and 65 months, and the ulcers remained the same size or enlarged very slowly. Yucel *et al.*[7] described the results of MRI in a group of seven patients, all of whom presented with chest and/or back pain. There had been a contained rupture in one patient. Three patients had surgical repair although the indications for surgery were not given; the rest were treated medically. Two of the medically treated patients were lost to follow-up but the other two remained clinically stable at 9 and 33 months. The latter had repeat MRI that revealed no change in the appearance of the aorta. Vilacosta *et al.*[5] reported the use of TOE for imaging ulcers in 12 patients, all of whom presented with chest and/or back pain. Five underwent operative repair, two for accompanying aneurysm and three for dissection. Two patients died as a result of rupture; five patients were managed medically and were alive after 3–24 months' follow-up.

The above provides a brief summary of the larger series published to date. At first sight the outcome for these patients seems quite diverse but on closer inspection some conclusions about the natural history of penetrating ulcers may be drawn. Stanson *et al.*[4] noted that seven of 16 patients had a contained rupture while Coady *et al.*[6] found a rupture rate of 40 per cent; these reports are in sharp contrast to the results of Harris *et al.*[9], who described no ruptures on long-term follow-up. The high incidence of rupture in Coady's patients has been attributed to the fact that the mean aortic diameter was 6·5 cm and that the rupture of the ulcer actually represented disruption of a thoracic aortic aneurysm[6]. Writing in a discussion at the end of their article, Coady *et al.* agreed that the 'size of the aorta should be an important additional guide to the management of these lesions'. Although rupture may be more likely in a dilated aorta, it may still occur through an ulcer in an aorta of normal size, as illustrated in the series of Vilacosta *et al.*[5] in which the two patients who died from rupture were not the patients with ulceration within an aneurysmal aorta.

Another important difference between studies is the proportion of patients who presented with chest and/or back pain. Twelve of Coady's 15 patients and 13 of Stanson's 16 patients presented with pain. In comparison, only four of Harris's 18 patients complained of pain, the rest of the ulcers being incidental findings on investigation for other conditions. So the presence of pain may indicate that there is an acutely evolving pathological process with a higher probability of life-threatening complications. If an ulcer becomes asymptomatic or is discovered incidentally, it might still be a cause for concern. Kazerooni *et al.*[8] followed four of 16 patients and detected an increase in aortic size after a mean interval of just 17 weeks. Harris *et al.*[9] had a longer period of observation (1–7 years); of 17 ulcers in ten patients, six progressed to saccular or fusiform aneurysms during this time. Progression of a similar proportion of ulcers (ten of 33) was noted by Quint *et al.*[13], although fewer patients developed aneurysmal disease.

Thus a picture of the natural history of penetrating ulcer emerges. Most are probably asymptomatic, with only a small number causing a clinical problem. It appears that if a patient presents with pain he or she is at significant risk of having or developing complications such as pseudoaneurysm or contained rupture, fistulation or even free rupture. During the next few days the pain may resolve as the ulcer stabilizes. Alternatively, the pain may continue or recur, which corresponds to progression of the pathological process and development of complications. If the pain settles and complications do not occur the ulcer may remain unchanged for many years, although there is a possibility of aortic dilatation and aneurysm formation, which has its own attendant risks.

Management

Whom to treat

With an increasing knowledge of the natural history of penetrating ulcer, a rational management plan based on current literature can be established[4,6,8,33]. Management strategies may be divided into those for symptomatic and those for asymptomatic ulcer. Once the diagnosis is made in a patient presenting acutely with chest and/or back pain, the patient should receive immediate intravenous analgesia to control pain and an antihypertensive agent to reduce blood pressure and so decrease the chance of rupture (*Fig. 4*)[6]. Those with a penetrating ulcer of the ascending aorta or arch should be considered a high-risk group; early operation has been recommended to prevent rupture[20]. If the pain resolves with medical therapy alone and there is no radiological evidence of deterioration, conservative management may be recommended. If this is adopted, oral antihypertensive therapy should continue if appropriate and imaging should be repeated within a few weeks to detect any silent progression of the disease. If a patient with a descending thoracic ulcer develops features of progression, early intervention is indicated. Such features include haemodynamic instability, persisting or recurrent pain and radiological evidence of deterioration (intramural haematoma expansion, pseudoaneurysm formation, pericardial effusion or bloody pleural effusion). Embolization from a penetrating ulcer is also considered to be an indication for repair[9].

Patients in whom an asymptomatic ulcer is found incidentally during investigation of an unrelated problem require a different approach. While the risk of acute problems seems low, there is a significant chance of progression of the ulcer over time, with or without associated aneurysm formation. Associated hypertension should be actively excluded and it seems prudent to monitor these patients with repeat imaging to detect any progression that may prompt future intervention.

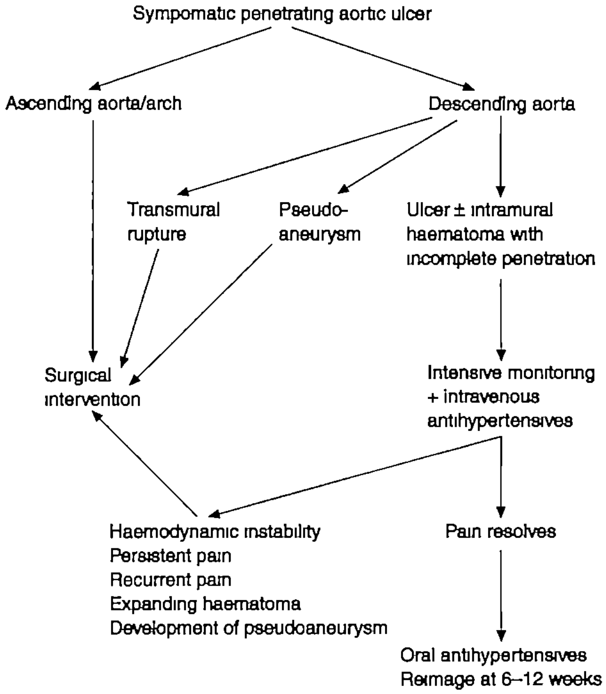

Fig. 4 Management of symptomatic penetrating atherosclerotic aortic ulcer. Modified from Movsowitz *et al.*[35]

Therapeutic options

The open operative repair of a penetrating ulcer requires local excision of the ulcer and graft interposition[2]. This is obviously a major undertaking in a population of patients with a high incidence of co-morbidity and so there is a high risk of both death and morbidity, including paraparesis and cerebrovascular accident[2,6]. Any desire to prevent the complications of a symptomatic ulcer by open surgery must be tempered with caution; the patient's fitness and the wishes of both patient and relatives must be considered.

Over the past decade there has been a rapid expansion in the use of endovascular stent-grafts to treat electively a variety of aortic diseases, including abdominal and thoracic aneurysms[36,37]. Such devices have also been used successfully in the emergency setting to treat acute descending thoracic aortic rupture from both aneurysm and trauma[38,39]. The use of stent-grafts for aortic ulcers was first described by Dake *et al.*[37] in 1994 in a paper reporting the use of this technique for thoracic aortic aneurysms of various aetiologies. Within the group of 33 patients with thoracic aneurysm were five cases of penetrating ulcer with an associated pseudoaneurysm. All five patients were treated successfully by the endovascular method (*Fig. 5*). Murgo *et al.*[11] reported their endovascular results in four patients. They were a frail group with a mean age of 76 (range 65–83) years and all had congestive cardiac failure. The ulcers were complicated in three cases by retrograde dissection, false aneurysm and rupture (one patient each). Endovascular stent-graft deployment was successful initially in all cases. However, one patient had a persisting perigraft leak that resolved spontaneously within the first month. A second patient developed a new false aneurysm 4 days after the original operation and this was treated with a second procedure 3 days later. One procedure was complicated by transient paraparesis secondary to spinal ischaemia but the overall the 30-day survival rate in this series was 100 per cent. Perhaps as a reflection of the frailness of this group, one patient died from pneumonia and cardiac failure 34 days after the operation. A further patient developed a pseudoaneurysm independent of the original ulcer within 3 months but refused further intervention and died suddenly at home from unknown causes 6 months after the endovascular procedure. In the remaining two patients no complications were observed during follow-up of 6 and 11 months. In 1999 Brittenden *et al.*[10] reported two cases of penetrating ulcer that were successfully treated endovascularly. The patients had presented acutely with chest pain and had haemothoraces. Both patients remained well at 1 year.

For the successful exclusion of a penetrating ulcer from the circulation there must be an adequate length of normal aorta above and below the lesion for the proximal and distal ends of the stent-graft to obtain purchase. Therefore the ulcer must not be adjacent to the left subclavian artery or the coeliac axis. Likewise, if the ulcer lies within an aneurysm there must be sufficient proximal and distal aneurysm neck for the stent to fasten to without impinging on these vessels. There must also be adequate access, preferably via the exposed common femoral artery. The size of the sheath required for stent-graft deployment varies between manufacturers but is usually around 25 Fr. If the femoral or iliac arteries are stenosed, excessively tortuous or merely small, access by this route may not be possible. Alternatives in this situation are insertion via an extraperitoneal approach to reach the common iliac artery or even the abdominal aorta[10,37]. During deployment, because the flow of blood along the aorta continues, the stent-graft may slip distally before the stent is fully expanded and fixed into position. To prevent this, pharmacological reduction in blood pressure has been advocated[10]. Should slippage occur and the ulcer remain insufficiently covered, a second stent may be safely deployed.

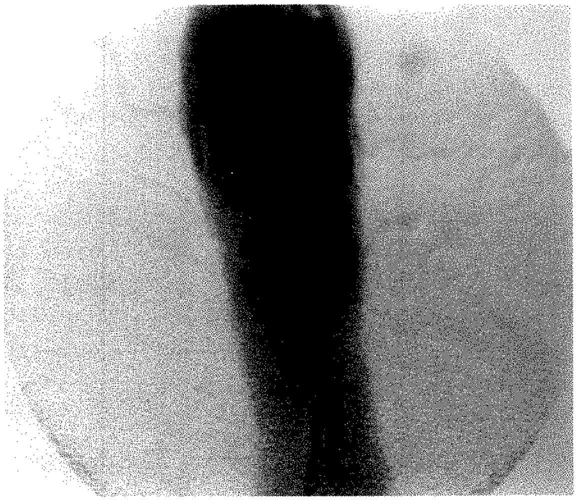

Fig. 5 Angiogram of patient in *Figs 1–3* after stent-graft deployment. Note that the ulcer is now excluded from the circulation

The type of surgical intervention has conventionally been open repair with its attendant morbidity and mortality rates. The use of endovascular stent-grafts to treat symptomatic descending thoracic aortic ulcer provides a less invasive alternative to open repair in these frail patients. In those who present acutely and show features of disease progression, the authors advocate the use of endovascular intervention. Conventionally, conservative treatment has been advocated for patients whose symptoms settle with medical therapy but, if the apparent safety of the endovascular technique is confirmed, such intervention may be increasingly considered in this group. However, more detailed information about the natural history of these lesions is needed and evidence of the long-term safety of stent-grafting is required. While endovascular stents may also be used for symptomatic embolization, for an incidentally discovered, asymptomatic, uncomplicated ulcer the authors recommend close observation with intervention only if the ulceration progresses. In any patient with a penetrating ulcer who is being regularly observed it must be remembered that there is a significant risk of aortic aneurysm formation at a site remote from the ulcer.

Conclusion

Our knowledge of penetrating aortic ulcer is still far from complete. The true incidence, detailed natural history and indications for treatment are likely to be the subject of continued research and debate. This article has summarized current understanding of this interesting condition and provides a practical management framework for its treatment. The use of endovascular stent-grafts to treat ulceration is still in its infancy and long-term results of large series are not yet available. Nevertheless, their use may be a useful addition to the possible interventions for penetrating ulcer, especially in high-risk patients.

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Prospective randomized double-blind placebo-controlled trial of glyceryl trinitrate in endoscopic retrograde cholangiopancreatography-induced pancreatitis

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Background: One possible aetiology of pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP) is cannulation-induced spasm of the sphincter of Oddi and consequent pancreatic duct obstruction. Sublingual glyceryl trinitrate (GTN) has been shown to produce periampullary sphincter relaxation. The aim of this study was to determine whether prophylactic long-acting GTN could reduce the incidence of ERCP-induced pancreatitis.
Methods: In a randomized double-blind study, prophylactic treatment with GTN (2 mg given sublingually 5 min before endoscopy) was compared with placebo in 186 patients who presented for elective ERCP. The primary endpoint was the occurrence of pancreatitis within 24 h, defined as a serum amylase concentration greater than 1000 units/ml in association with a visual analogue pain score of more than 5.
Results: The incidence of pancreatitis was lower in the GTN group compared with placebo (seven of 90 *versus* 17 of 96; $P < 0.05$). Mean serum amylase values were similar in the two groups. The protective effect of GTN appears to be highest in the diagnostic ERCP group (one of 54 *versus* ten of 66; $P = 0.012$) and in the group in which cholangiography alone was performed (one of 54 *versus* eight of 57; $P = 0.032$).
Conclusion: Prophylactic treatment with GTN reduces the incidence of pancreatitis following ERCP but does not seem to reduce the extent of hyperamylasaemia or the severity of pancreatitis.

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is now well established in the diagnosis and treatment of pancreatobiliary disease. Pancreatitis remains one of the most feared complications of ERCP, with a frequency ranging from 1 to 40 per cent depending partly on the chosen definition of pancreatitis[1]. The aetiology of ERCP-induced pancreatitis is unclear. The most commonly held, but largely unproven, hypothesis is that the injury initiating pancreatitis in this setting is predominantly mechanical, resulting from cannulation-induced spasm of the sphincter of Oddi and consequent temporary pancreatic duct obstruction[2]. Prophylactic administration of calcium channel blockers such as nifedipine to reduce sphincter of Oddi spasm failed to show a benefit in reducing post-ERCP pancreatitis[3]. This lack of effect was attributed to incorrect timing and inadequate dosage of nifedipine[3].

Staritz *et al.*[4] demonstrated that sublingual glyceryl trinitrate (GTN), a nitric oxide donor, lowered basal pressure and contraction amplitude in the sphincter of Oddi. The same investigators subsequently used this information for endoscopic removal of common bile duct stones of between 6 and 12 mm in diameter through intact papillae after a medical sphincter dilatation using GTN[5]. Another randomized controlled trial showed improved cannulation at ERCP after sublingual GTN[6]. Increasing difficulty of cannulation is thought to be an independent risk factor for pancreatitis after ERCP[7].

It could be hypothesized that prophylactic long-acting GTN, by producing prolonged relaxation of the sphincter of Oddi and by improving the ease of cannulation, would reduce the incidence of post-ERCP pancreatitis. A prospective placebo-controlled double-blind randomized trial was conducted to test this hypothesis.

Patients and methods

The institutional ethics committee and the Medicines Control Agency approved the study. Informed consent was obtained from all patients. The study was conducted at the Countess of Chester Hospital from October 1995 to December 1997. Eligible patients were those aged 18 years and over who were scheduled to undergo ERCP and, when indicated, endoscopic sphincterotomy, stone removal or stent placement. Patients with active acute pancreatitis or chronic pancreatitis and those already taking nitrate-containing medication were excluded.

Randomization was by computer-generated numbers, details of which were concealed in sequentially numbered, sealed, opaque envelopes. Each patient was randomized to receive either 2 mg sublingual GTN as buccal tablets (Suscard Buccal®; Pharmax, Bexley, UK) or placebo 5 min before the procedure under double-blind conditions. Tablets containing GTN or placebo were identical in appearance and taste. The details of the code for the drug and placebo were held by the pharmacy department, which maintained them until the end of the trial. Intravenous cefuroxime 750 mg (Zinacef®; Glaxo Wellcome, Uxbridge, UK) was given as a preoperative antibiotic to all patients. Before ERCP all patients received premedication consisting of intravenous pethidine hydrochloride 50 mg and diazepam (Diazemuls®; Dumex, Barnstaple, UK) titrated to age and tolerance. Hyoscine butylbromide 20 mg (butylscopalamine, Buscopan®; Boehringer Ingelheim, Bracknell, UK) was also administered intravenously at the first view of the ampulla to inhibit duodenal peristalsis.

Meglumine diatrozate (Urograffin 150; Schering, Berlin, Germany), a non-ionic, low osmolar dye, was used to delineate the duct systems throughout the study. A single endoscopist (P.R.E.) performed all the procedures using either an Olympus TJF200 or JF200 duodenoscope (Olympus Optical, Tokyo, Japan). Cannulation was undertaken with a standard-tip reusable cannula (Hobbs Medical, Stafford Springs, Connecticut, USA) or a contour tapered-tip cannula (Boston Scientific, Natick, Massachusetts, USA). When indicated, sphincterotomy was performed using an Ultratome XL long-nose sphincterotome (Boston Scientific). Endoprosthesis placement, when required, was performed in the conventional manner using a plastic prosthesis for the bile duct. At the end of the procedure the endoscopist recorded the details of the endoscopic manoeuvres performed, whether the pancreatic duct, bile duct or both were opacified, and whether the cannulation was superficial or deep.

Serum amylase concentration was measured before endoscopy and 6 h after the procedure. All patients were kept in hospital for 24 h and the amylase level was determined again at 12 and 24 h if the patient had persistent abdominal pain.

A visual analogue pain score was completed at 6 h by the patient. If abdominal pain had occurred after 6 h, the pain score was filled in at the time of occurrence of pain. The location of pain was specified as abdominal or back pain, and the pain scale was constructed with scores ranging from 0 (no pain) to 10 (unbearable pain).

The primary endpoint of the study was the development of pancreatitis within 24 h of ERCP. Acute pancreatitis was defined as a serum amylase level greater than 1000 (normal range 5–300) units/ml at 6 h in association with a visual analogue pain score of more than 5. Deep cannulation was defined as entry of the cannula into the relevant duct allowing free movement of the cannula within that duct. Superficial cannulation was defined as entry of the cannula allowing delineation of the duct with dye but not free movement of the cannula within.

A sample size of 200 patients was planned; at least 180 were needed. This number would be sufficient to detect an assumed reduction in the incidence of pancreatitis from 20 per cent in the placebo group (estimated from hospital data for the previous year) to 5 per cent in the GTN group, with 80 per cent power in a two-sided test at a 5 per cent significance level. χ^2 and Fisher's exact tests were used as appropriate for comparison of categorical data. The Mann–Whitney *U* test was used for comparison of continuous variables. Significance was defined as $P < 0{\cdot}05$.

Results

Of a total of 208 patients, 101 were randomized to receive placebo and 96 to receive GTN. ERCP was not technically possible in 11 patients (*Fig. 1*). Complete data were available for 96 patients who received placebo and for 90 who received GTN. In these 186 patients, the common bile duct or pancreatic duct, or both, were opacified. The cannulation rate for ducts that ERCP had been specifically required to visualize was similar in both groups: 84 (93 per cent) of 90 in the GTN group and 88 (92 per cent) of 96 in the placebo group. Comparison of age, sex and indication for ERCP showed no significant difference between the two groups (*Table 1*). The details of cannulation at ERCP, mean amylase levels and associated endoscopic procedures performed are shown in *Table 2*. There was no significant difference between the two groups in the cannulation rate, mean amylase concentration or number of therapeutic procedures undertaken.

Some 24 patients (13 per cent) developed pancreatitis: seven (8 per cent) in the GTN group and 17 (18 per cent) in the placebo group ($P < 0{\cdot}05$). Between the GTN and placebo groups in patients who developed pancreatitis,

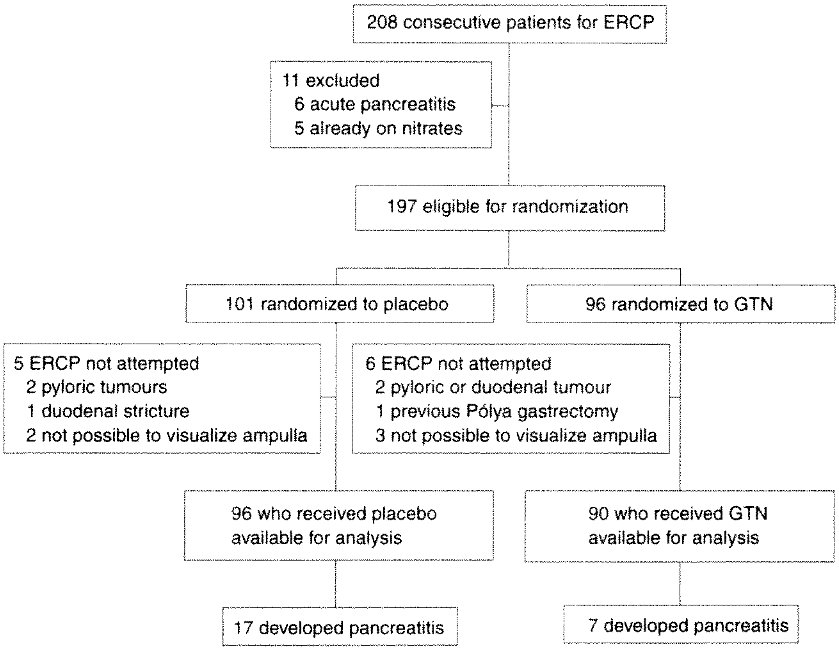
208 consecutive patients for ERCP
11 excluded
6 acute pancreatitis
5 already on nitrates
197 eligible for randomization
101 randomized to placebo
96 randomized to GTN
5 ERCP not attempted
2 pyloric tumours
1 duodenal stricture
2 not possible to visualize ampulla
6 ERCP not attempted
2 pyloric or duodenal tumour
1 previous Pólya gastrectomy
3 not possible to visualize ampulla
96 who received placebo available for analysis
90 who received GTN available for analysis
17 developed pancreatitis
7 developed pancreatitis

Fig. 1 Study profile. ERCP, endoscopic retrograde cholangiopancreatography; GTN, glyceryl trinitrate

Table 1 Baseline characteristics of the two groups

	GTN (n = 90)	Placebo (n = 96)
Mean (range) age (years)	63·7 (19–90)	63·7 (28–89)
Sex ratio (M : F)	22 : 68	36 : 60
Indication for ERCP		
Biliary obstruction or stenosis	18	23
Choledocholithiasis	28	30
Previous acute pancreatitis	20	15
Before laparoscopic cholecystectomy to exclude CBD stones	24	28

CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; GTN, glyceryl trinitrate

Table 2 Details of cannulation and endoscopic procedures in the two groups

	GTN	Placebo
Bile duct cannulation		
Superficial cannulation	14	16
Deep cannulation	70	72
Not cannulated	6	8
Pancreatic duct cannulation		
Superficial cannulation	21	22
Deep cannulation	15	17
Not cannulated	54	57
Both pancreatic and bile duct cannulation	30	31
Endoscopic procedure		
Sphincterotomy and stone extraction	27	21
Stenting of bile duct	9	9
Amylase level (units/ml)*		
Mean(s.e.m.)	834(221)	850(155)
Median(s.d.)	247(1877)	252(1375)

*Normal range 5–300 units/ml. GTN, glyceryl trinitrate. There were no significant differences between the two groups

there was no significant difference in the bile duct cannulation (6 *versus* 13) or pancreatic duct cannulation (6 *versus* 11). In the GTN group, of the seven patients who developed pancreatitis, four had sphincterotomy and stone extraction and two had biliary duct stenting, whereas in the placebo group, of the 17 who developed pancreatitis, five had sphincterotomy and stone extraction and two had biliary duct stenting (P not significant, Fisher's exact test). The mean(s.e.m.) amylase level in those who had pancreatitis in the GTN and placebo groups was 4130(807) and 2856(429) units/ml respectively (two-sided P = 0·43, Mann–Whitney U test). The corresponding median(s.d.) amylase values were 2500(3520) and 2123(1778) units/ml respectively. When the procedure involved only cholangiography, without delineation of the pancreatic duct, the incidence of pancreatitis was significantly reduced in the GTN group compared with placebo (P = 0·032). Likewise the incidence of pancreatitis in the diagnostic ERCP group compared with that in patients who had therapeutic ERCP was significantly reduced in those who received GTN

Table 3 Proportion of patients with pancreatitis following different procedures

	No. of patients with pancreatitis			
Procedure	GTN	Placebo	Total	P*
Cholangiography only (ERC)	1 of 54 (2)	8 of 57 (14)	9 of 111 (8)	0·032
Pancreatography only (ERP)	1 of 6 (17)	2 of 8 (25)	3 of 14 (21)	n.s.
Both pancreatography and cholangiography (ERCP)	5 of 30 (17)	7 of 31 (23)	12 of 61 (20)	n.s.
Therapeutic ERCP	6 of 36 (17)	7 of 30 (23)	13 of 66 (20)	n.s.
Diagnostic ERCP	1 of 54 (2)	10 of 66 (15)	11 of 120 (9)	0·012

Values in parentheses are percentages. ERC, endoscopic retrograde cholangiography; ERP, endoscopic retrograde pancreatography; ERCP, endoscopic retrograde cholangiopancreatography; n.s., not significant. *Two-sided χ^2 test (Fisher's exact test if total number was less than 20)

(P = 0·012) (*Table 3*). When all the patients were analysed together, therapeutic ERCP had 2·4 (95 per cent confidence interval 1·02–5·79) times the risk of inducing pancreatitis compared with diagnostic ERCP.

None of the patients in this study developed severe pancreatitis as defined by Ranson criteria[8]. In all patients the pancreatitis settled with conservative management and no one required radiological or surgical intervention. None of the patients who developed pancreatitis in this study required parenteral nutrition and, although many were initially transferred to the high dependency unit, the mean length of stay was approximately 4 days in both groups. The relatively small number of patients precludes statistical analysis.

The only significant adverse effects attributable to GTN were hypotension and headache. More than 50 per cent of the treatment group suffered a period of hypotension (systolic brachial pressure lower than 100 mmHg) in the immediate postprocedural period, compared with 5 per cent of the placebo group. The hypotension responded in all cases to an intravenous infusion of crystalloids. A small number of patients in the treatment group complained of headache.

Discussion

The risk of pancreatitis induced by ERCP cannot at present be eliminated. Almost certainly, the aetiology of ERCP-induced pancreatitis is multifactorial. Spasm of the sphincter of Oddi, forceful injection of the dye, chemical toxicity from the hyperosmolar ionic contrast and bacterial contamination of the pancreatic duct have all been suggested[9,10]. Attempts to prevent this complication by using non-ionic contrast agents[11] or the prophylactic administration of aprotinin[12], glucagon[13], calcitonin[14], nifedipine[15], somatostatin[16] and octreotide[17] have been disappointing. In a large prospective study gabexate, a protease inhibitor, showed a fourfold reduction in post-ERCP pancreatitis compared with placebo[18]. However, the high cost of this agent coupled with the need for continuous infusion over 12 h has restricted its routine use for this purpose. Manometric studies with GTN have shown a marked reduction in the basal tone of the sphincter of Oddi muscle, widening of the papillary lumen and a diminution in the resistance to bile flow, all lasting for 15 min after GTN administration[4]. This dilating effect of GTN on the sphincter of Oddi has been used for two purposes: to remove small and medium-sized common bile duct stones through intact papillae[5] and to facilitate cannulation of the ampulla in diagnostic ERCP[6]. In addition to its physiological actions, the further benefits of GTN are that it can be administered as a buccal tablet and it is inexpensive: 100 2-mg tablets cost approximately £14·00.

This is the first study specifically to demonstrate a significant diminution in post-ERCP pancreatitis with long-acting GTN. As the systemic effects of GTN in the form of buccal tablets last for 6 h, all the effects of GTN on the sphincter of Oddi can be assumed to persist for a comparable period. Prolonged relaxation of the sphincter of Oddi probably opposes sphincter of Oddi spasm induced by the mechanical trauma of ERCP, thereby reducing the incidence of pancreatitis.

Subgroup analysis showed the protective effect of GTN to be maximal in the diagnostic ERCP group and when cholangiography alone was performed. It may be that GTN exerts its effect only when the mechanical trauma induced by ERCP is mild or moderate. More severe trauma may disrupt the pancreatic ducts or even rupture the acinar units, with the release of activated enzymes and inexorable progression to pancreatitis. The emergence of magnetic resonance cholangiopancreatography (MRCP) in the diagnosis of pancreatobiliary disease is likely to have a significant impact on the use of ERCP in the future[19]. This is predominantly expected to reduce the number of diagnostic ERCPs. MRCP and contrast-enhanced computed tomography in the authors' institution, however, have not been as helpful in the diagnosis of biliary disease as might be suggested by the current literature. It is likely, however, that the number of diagnostic ERCPs will fall over the next few years, perhaps resulting in a diminishing potential role for prophylactic GTN.

The incidence of pancreatitis in the placebo group was higher (18 per cent) than that reported in many series[3,11–17]. This may have been due to the liberal criteria used to define pancreatitis. As mentioned in other studies, the problem of defining pancreatitis has led to a great deal of interstudy variability[16]. To provide a consistent approach across different studies, the criteria adopted in this study were both acceptable and robust, although still somewhat subjective.

In summary, GTN when given 5 min before ERCP appears to be effective in reducing post-ERCP pancreatitis. However, because of the relatively small sample size, convincing evidence has not been provided that this reduces the severity of pancreatitis and degree of hyperamylasaemia or increases the rate of cannulation. Further controlled studies of GTN administration as a prophylaxis against pancreatitis in patients undergoing ERCP are required to confirm its promising therapeutic role in this setting.

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Randomized clinical trial comparing totally extraperitoneal inguinal hernia repair with the Shouldice technique

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Background: The optimal technique for inguinal hernia repair remains contentious. This study compared the Shouldice repair with the totally extraperitoneal endoscopic (TEP) method in a randomized clinical trial, with quality of life (QoL) and cost analysis.

Methods: Two hundred patients were randomized to Shouldice or TEP repair. Patients were assessed after operation by questionnaire to determine operative outcomes, complications, QoL, and return to work and normal lifestyle.

Results: There were 117 TEP and 115 Shouldice repairs. Median operating time was longer for TEP repair (70 *versus* 56 min; $P = 0.0001$), but patients were discharged earlier (68 *versus* 48 per cent within 1 day; $P = 0.0065$), and had a quicker return to work (14 *versus* 30 days; $P = 0.0001$) and normal lifestyle (21 *versus* 35 days; $P = 0.0001$). Open repair was nearly 40 per cent cheaper. Late follow-up in 171 patients (86 per cent) at a median of 1·3 years found that TEP repair led to fewer complications at 1 year (9 *versus* 21 per cent; $P = 0.05$) and was associated with significant improvement for the QoL components of work performance and satisfaction, physical symptoms and sense of well-being.

Conclusion: TEP repair results in fewer complications and an earlier return to work and normal lifestyle, but is more expensive and takes longer to perform.

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Introduction

The optimal method of providing a durable, low-morbidity repair of inguinal hernia remains a matter of contention[1–3]. The ideal repair should allow a patient a rapid return to normal work, leisure and recreation at a reasonable cost to the patient and the wider community.

Various methods of open repair, using either tissue suture or reinforcement with a prosthesis, have been championed for years, often by way of large series from a single institution[1,2]. Laparoscopic and endoscopic techniques, which have evolved during the past decade, have been employed more recently, but not without controversy or conflicting results[3–6].

The aim of this study was to compare the Shouldice sutured hernia repair with the totally extraperitoneal endoscopic (TEP) method, using a randomized clinical trial.

Patients and methods

Patients seen in the outpatient department at the Austin and Repatriation Medical Centre, Melbourne were invited to participate in the trial. After giving informed consent, they were randomized to either TEP repair or the Shouldice technique. Allocation was by random numbers and was stratified for the employment status of the patients.

Patients were excluded for the following reasons: emergency hernia surgery for obstruction or strangulation, incarcerated or irreducible hernia, inability to speak English, history of dementia or psychotic illness, refusal to give informed consent, or being unfit for general anaesthesia. Two hundred patients were randomized and the surgery was performed between 1993 and 1997.

A research nurse specially allocated to the study visited the patients before operation and baseline data were gathered relating to lifestyle, employment, medical status and hernia-related symptoms.

Hernia repair

The operations were undertaken by one of three surgeons or their trainees from one team in a university teaching hospital. Open and endoscopic procedures were both performed under general anaesthesia and all patients received local anaesthetic infiltration of the wounds. All patients were admitted to a ward after operation for trial assessment.

The Shouldice technique[7] was used in the open surgery group. The hernia was exposed through a groin incision and, after division of the cremaster muscle, the hernia sac was opened, emptied, ligated at the deep ring and excised. The transversalis fascia was incised and then overlapped with two layers of 2/0 polypropylene (Prolene; Johnson and Johnson Medical, North Ryde, New South Wales, Australia) sutures. The conjoint tendon was apposed to the inguinal ligament with two layers of 2/0 polypropylene and the external oblique was closed in one layer over the cord with 2/0 polyglactin (Vicryl; Johnson and Johnson).

For TEP repair, initial access to the preperitoneal space was gained via a short infraumbilical incision. Thereafter, the space was enlarged using either laparoscopically assisted blunt dissection or a disposable balloon dissector (Origin Medsystems, Menlo Park, California, USA). The first 42 procedures were done with blunt dissection, but from 1995 the balloon dissector was used exclusively. The preperitoneal space was maintained by insufflation of carbon dioxide at 12 mmHg and a 30° laparoscope was used. Two further working ports were inserted in paramedian positions, one suprapubic and one midway between the pubis and umbilicus. Using a combination of sharp and blunt dissection the hernia was reduced and cord structures identified. A 10 × 15-cm piece of polypropylene mesh was then positioned to cover the entire myopectineal orifice and secured in position, either with staples or a hernia tacker (Origin Medsystems). A slit was not made in the mesh. The posterolateral edge of the mesh was not fixed, to avoid damage to the lateral cutaneous nerve of the thigh.

The duration of the operation, conversion rates and intraoperative complications were recorded.

No special instructions were given to the ward medical and nursing staff regarding care of the patients after operation. Postoperative pain was recorded using a visual analogue scale. Narcotic and non-narcotic analgesics were administered as necessary and the number of doses of each was recorded. All patients were mobilized as soon as possible, and early discharge was encouraged. The length of hospital stay was recorded. Patients were advised to return to work and recreational activities at their own pace.

Follow-up

Patients were visited by the research nurse immediately before discharge, and at 1 week, 1 month and 1 year after operation. A telephone interview took place after 3 months. The surgical team assessed each patient at 1 week and 1 month, and an independent surgeon, who had not performed any of the operations, reviewed the patients at 1 year.

At each visit patients were examined and data were collected regarding postoperative recovery, time to return to work and normal lifestyle, pain and analgesic requirements, and the presence of complications involving the wound, urinary tract, testicles or peripheral nerves. In addition, an assessment was made of their quality of life (QoL) at each visit using a standard questionnaire. At the 1-year examination special attention was paid to any sign of recurrent or contralateral hernia.

Quality of life analysis

QoL after each operation was compared using an adaptation of a standard scale[8]. This was analysed from questionnaires administered at 1 week, 1 month and 3 months for general well-being, physical symptoms, sleep dysfunction, work performance, emotional status and sexual function[9–13].

A final score for each patient within each component and time interval (1 week, 1 month and 3 months) was calculated as the mean of the scores received on each of the questions. Higher scores represented poorer outcomes. A Poisson regression analysis (adjusted for correlations that occur within person by using the *xtgee* command in Stata 6.0 (Stata Corporation, College Station, Texas, USA)) was then used to model a final score as a function of treatment (with a reference category of open surgery) and time, controlling for the covariates of physical employment, age and smoking status. The exponential of the regression coefficients from a Poisson regression provided estimates of rate ratios for the independent variables.

Cost analysis

A study was made of the costs in each group, using a representative sample of five patients chosen at random, but similar with respect to age, hernia history and state of health. Hospital costs were determined by the authors' own method, as published previously[14], analysing both the direct costs (salaries, equipment, laboratory and radiology costs and consumables) and the indirect costs (hospital overheads, operating suite costs), excluding depreciation. The conversion rate is approximately £1 to Australian $2·5.

Statistical analysis

Patients were analysed by the principle of intention to treat, so that the results of patients whose operation was converted from endoscopic to open surgery were analysed in the endoscopic group. The Mann–Whitney *U* test was used for comparison of medians; Student's t test was used for normally distributed data with equal variance between the two groups. The χ^2 and Fisher's exact tests were used for contingency tables. Statistical significance was assumed when $P < 0{\cdot}05$; no adjustment for multiple testing was carried out.

A power calculation was performed to estimate sample size. A minimum of 183 patients in total was required to give an 80 per cent power of detecting an improvement from 30 to 50 per cent in the proportion of patients who returned to a normal lifestyle at 1 month ($\alpha = 0{\cdot}05$). The sample size was not sufficient reliably to detect differences in recurrence rates, unless the difference was very large.

Results

Patient demographics and hernia types

Two hundred patients underwent 231 hernia repairs (32 bilateral). Some 98 per cent of patients were men and patients in both operative groups were of similar age, employment status, weight and smoking history (*Table 1*). In all, 116 TEP and 115 Shouldice repairs were performed; the type and side of hernia were well matched between the two operations.

Perioperative events

The median duration of operation was 70 (range 32–160) min for TEP repair and 56 (range 30–145) min for Shouldice repair ($P = 0{\cdot}0001$). The endoscopic repair took longer to perform for both single and bilateral hernias.

Table 1 Patient demographics and hernia details

	TEP	Shouldice
Mean age (years)	51	53
Employed (%)	44 (34)	45 (34)
Smoker (%)	31	29
Mean weight (kg)	75	75
Type of hernia		
Right inguinal		
Direct	19	14
Indirect	45	48
Pantaloon	3	1
Total	67	63
Left inguinal		
Direct	12	18
Indirect	37	31
Pantaloon	0	3
Total	49	52
Recurrent	8	4
Bilateral	17	15

Values in parentheses are the percentage in physical employment. TEP, totally extraperitoneal endoscopic repair

There were 12 conversions from endoscopic to open repair; all but one took place early in the study before the routine use of the dissection balloon. The reasons for conversion were large peritoneal tears (four), bleeding (three), inability to reduce the hernia (two), poor endoscopic view (two) and obesity (one). There was no death, visceral or vascular intraoperative injury, and no early unplanned return to the operating theatre in either group.

Recovery

Sixty-eight per cent of patients in the TEP group were discharged within 1 day of surgery compared with 48 per cent in the open group ($P = 0{\cdot}0065$) (*Table 2*). Mean pain scores were lower immediately after TEP repair and at 1 week, although the difference reached significance only at 1 week. Patients who had open surgery required significantly more oral analgesia before discharge ($P = 0{\cdot}02$).

Recovery in the community was significantly quicker after TEP hernia repair (*Table 3*). Patients in this group returned to work after a median of 14 days compared with 30 days after Shouldice repair, irrespective of whether the patients were self-employed or employees. Similarly, patients who had TEP repair required less analgesia at home and returned to their normal lifestyle more rapidly.

Table 2 Early postoperative recovery after hernia repair

	TEP	Shouldice	P
Postoperative hospital stay < 24 h (%)	68	48	0·0065
Pain score*			
Immediately after operation	3·7(1·8)	4·3(1·9)	0·058
After 1 week	2·1(1·8)	2·9(2·0)	0·0065
Analgesia in hospital			
Narcotics (%)	39	50	0·18
More than two doses oral analgesic (%)	53	70	0·02

*Values are mean(s.d.). TEP, totally extraperitoneal endoscopic repair. Student's t test

Table 3 Recovery in the community after hernia repair

	TEP	Shouldice	P
Outpatient analgesia (days)*	2 (0–21)	7 (0–28)	0·0001
Return to work (days)*	14 (3–42)	30 (7–84)	0·0001
Return to normal lifestyle			
Time to return (weeks)*	3 (1–21)	5 (1–28)	0·0001
Within 1 month (%)	77	49	0·0002

*Values are median (range). TEP, totally extraperitoneal endoscopic repair. Mann–Whitney U test

Table 4 Quality of life after totally extraperitoneal endoscopic repair compared with Shouldice repair, and improvement after the operation

		Surgery*		Time (weeks)	
Quality of life	No.†	Rate ratio‡	*P*	Rate ratio‡	*P*
Performance and satisfaction	151	0·87 (0·76–1·00)	0·046	0·82 (0·81–0·84)	< 0·001
Physical symptoms	171	0·78 (0·64–0·95)	0·015	0·84 (0·82–0·86)	< 0·001
Sexual function	163	0·89 (0·53–1·50)	0·668	0·97 (0·95–1·00)	0·019
Sleep disorder	192	0·72 (0·35–1·46)	0·358	0·96 (0·93–0·99)	0·010
Sense of well-being	192	0·71 (0·54–0·94)	0·016	0·87 (0·84–0·90)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *Reference category open surgery. †Number of individuals interviewed at least once (mean number of times each participant interviewed was 2·7). ‡Adjusted for age, smoking status and physical employment

Quality of life

There was a significant improvement in the final QoL score after TEP hernia repair compared with open surgery for the components work performance and satisfaction (13 per cent reduction), physical symptoms (22 per cent reduction) and sense of well-being (29 per cent reduction) (*Table 4*). Patients in both surgical groups, however, gained significant improvement with time for all QoL components. Although at each time point the median QoL score was better for the TEP repair group, this was not significant.

Complications and recurrence

At 1-week follow-up, complications were recorded after 16 per cent of endoscopic repairs compared with 36 per cent after Shouldice repair ($P = 0{\cdot}028$). These complications were mainly minor, such as bruising or wound paraesthesia; however, there were four major haematomas in the open repair group compared with two in the TEP group. Similarly, there were more wound infections after Shouldice repair (seven) than after TEP repair (one).

At 1-month follow-up most complications had resolved, but 7 per cent in the TEP repair group still had at least one complication, compared with 19 per cent of patients who had Shouldice repair ($P = 0{\cdot}025$). Five patients in the open repair group had persistent problems with wound infection. Numbness was reported by eight patients who had open surgery compared with two who had a TEP repair.

Late follow-up was completed for 171 patients (86 per cent) at a median interval of 1·3 years. Twenty-nine patients were lost to follow-up, 20 after TEP repair and nine from the open surgery group. Of these patients, 13 had either died or had severe health problems (non-hernia related) which prevented their participation, three had moved to another city, seven were untraceable and six refused to attend. Patients who had a TEP repair were significantly less likely to have a complication at 1 year than those who had a Shouldice repair: 9 *versus* 21 per cent ($P = 0{\cdot}05$). A higher rate of numbness (at various sites) was observed after open repair (14 patients) than after TEP repair (three) ($P = 0{\cdot}028$).

With respect to hernia recurrence at late follow-up, there were two recurrences after 93 laparoscopic repairs (2 per cent), compared with five after 106 Shouldice repairs (5 per cent). This difference was not statistically significant ($P = 0{\cdot}455$), as this study was not adequately powered to detect differences in recurrence rates of this magnitude. The two recurrences seen after TEP repair occurred in the same patient, who had a bilateral hernia. In addition, there was an ipsilateral femoral hernia in one patient in the open repair group.

Costs

The mean cost for Shouldice repair was $4249 and that for TEP repair was $5808, a difference of nearly 40 per cent. The main difference was in the cost of laparoscopic equipment and disposables; Shouldice repair cost a mean of $142 while TEP repair cost a mean of $1019.

Discussion

This trial commenced when laparoscopic hernia repair was in its infancy and was designed to compare the 'gold standard' for sutured open repair (Shouldice technique) with the totally extraperitoneal mesh hernioplasty.

The ideal method of open hernia repair is still debated. The Shouldice technique has been widely accepted as the best sutured repair following large case series[1,7] and randomized trials comparing it with other sutured repairs[15,16]. At the time this study commenced, the Shouldice technique was used by the authors in preference to a mesh repair. However, mesh 'tension-free' repair such as the Lichtenstein technique[2] appears to have similar advantages to the Shouldice technique in terms of quick recovery time, low recurrence rate and ease of performance[17–19].

Endoscopic hernia repair has been compared with a number of open repair methods, but these studies have produced confusing results[20–24]. Schrenk *et al.*[20] failed to demonstrate any significant benefit from either the laparoscopic or endoscopic approach. In general, however, laparoscopic and endoscopic repairs appear to offer the benefits of less postoperative pain, and faster return to work and normal activities, compared with open repair[21–24]. In addition, the incidence of complications tends to be higher in open operations[22]. The present study confirmed these findings, with a significantly lower complication rate at 1 week, 1 month and 1 year following TEP repair.

Comparative recurrence rates for endoscopic and open repairs have been published[20–25], but sample sizes are generally small and follow-up is short, so these studies had little power to detect differences of clinical importance. Liem *et al.*[24] documented a lower recurrence rate in the endoscopic group at 12 months, and Topal and Hourlay[25] reported a recurrence rate of 0·3 per cent at 1 year. The present study was unable to detect a statistical difference. Recurrence rates may be related to the experience of the surgeon. Endoscopic surgery has a long learning curve, with a higher rate of failure in the early stages of the learning experience. Liem *et al.*[24] noted that inexperience led to a high rate of hernia recurrence in the first year and stated that the skill and experience required to perfect the laparoscopic technique should not be underestimated.

Several authors[20,25,26] have suggested that endoscopic hernia repair may be better than open surgery for recurrent or bilateral hernias. There is little controlled evidence to support this contention, however, and confining the technique to this small group has implications in surmounting the learning curve.

Endoscopic hernia repair is more expensive, largely owing to the use of disposables[21,22], which has cost implications for health services. Offsetting this increased cost is the shorter hospital stay and earlier return to work, plus a potential saving in the case of bilateral hernias, which can be repaired simultaneously, negating the need for two admissions.

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Expression of inducible nitric oxide synthase contributes to the development of pancreatitis following pancreatic ischaemia and reperfusion

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Background: Inducible nitric oxide synthase (iNOS) activity is increased in experimentally induced acute pancreatitis. Increased expression of this isoform of nitric oxide synthase has been demonstrated in several organs subjected to ischaemia–reperfusion injury. The present experiment investigated the expression of iNOS and the effect of selective iNOS inhibition in pancreatic ischaemia–reperfusion.

Methods: Wistar rats ($n = 40$) were randomly and equally assigned to four groups. Groups 2 and 4 underwent 60 min of total pancreatic ischaemia followed by 6 h of reperfusion (I–R). Groups 1 and 3 underwent sham operation. The selective iNOS inhibitor L-N^6-(1-iminoethyl)-lysine (L-NIL) was administered to groups 3 and 4. Expression of iNOS was examined by immunohistochemistry. Other investigations included measurement of serum amylase activity and pancreatic wet : dry weight ratio, and histopathological examination.

Results: Eight of ten rats in group 2 (I–R only) expressed iNOS but none of the ten animals in group 1 (sham laparotomy) did so. Group 4 (I-R + L-NIL) animals had significantly lower serum amylase levels and wet : dry weight ratios than those in group 2 (I–R only). Microscopic evidence of pancreatic injury was present only in rats in group 2 (I–R only).

Conclusion: Expression of iNOS during reperfusion following pancreatic ischaemia contributes significantly to the development of acute pancreatitis.

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Introduction

Pancreatic transplantation is frequently complicated by the development of acute pancreatitis[1], largely as a result of ischaemia–reperfusion (I–R) injury secondary to cold preservation[2]. During the reperfusion period, endothelial dysfunction, activation of endogenous enzymes, leucocyte recruitment and activation all lead to the generation of oxygen-derived free radicals[2,3]. These processes promote lipid peroxidation while depleting glutathione and other sulphydryl compounds, leading to the development of pancreatitis. Treatment with antioxidants has been shown to reduce acinar cell injury and oedema in animal models of acute pancreatitis[3], implying an important role of oxidative stress in the disease process in general.

Nitric oxide, a hydrophobic gaseous molecule, is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS). Two principal forms of NOS have been described. A constitutive form, expressed in neuronal and endothelial cells (eNOS), is dependent on intracellular calcium levels for its activity. Inducible NOS (iNOS) may be expressed by a number of cells, usually in response to inflammatory mediators, and is independent of calcium for its activity[4]; iNOS produces nitric oxide at magnitudes several orders greater than the constitutive form and so may have a more important pathological role. Nitric oxide may be oxidized to nitrate and nitrite; otherwise it may lose an electron to form the nitrosonium ion, which can combine with the superoxide radical to form peroxynitrite, a highly active free radical[4].

Nitric oxide has various functions which may be broadly divided into two categories, proinflammatory and anti-inflammatory. Most of the proinflammatory functions are the result of nitric oxide acting as a free radical and include nitrosylation of iron–sulphur groups and tyrosine residues, inactivation of haem and lipid peroxidation. Anti-inflammatory effects are the result of guanylate cyclase activation (leading to reduced platelet and inflammatory cell activity and smooth muscle relaxation) or inhibition of the nuclear transcription factor κB (leading to decreased expression of a wide range of proinflammatory cytokines and adhesion molecules)[4]. Endothelial dysfunction and a fall in reduced nicotinamide adenine dinucleotide phosphate (NADPH) and oxygen content as a consequence of ischaemia lead to nitric oxide depletion during the early reperfusion period. By 6 h from the onset of reperfusion, activation of iNOS, by early release of inflammatory mediators such as tumour necrosis factor α, results in an increase in nitric oxide concentration[4]. It is not yet clear whether this increased production of nitric oxide following reperfusion is beneficial or detrimental to the pancreas.

In a rat model of pancreatic transplantation, Vollmar *et al.*[5] showed that L-arginine improves microvascular perfusion and attenuates pancreatic oedema and neutrophil infiltration. However, their study was limited to a reperfusion period of 2 h, when endogenous production of nitric oxide would be expected to be subnormal and iNOS would not yet have been expressed. On the other hand, Pi *et al.*[6] demonstrated that NOS inhibition attenuates pancreatic injury following transplantation. In a rat model of caerulein-induced pancreatitis there was decreased constitutive NOS activity and increased iNOS activity, together with evidence for peroxynitrite-mediated protein damage in the pancreas. These findings suggest that excess production of nitric oxide arising from iNOS may be partly responsible for the pathological changes of acute pancreatitis[7]. For the present study, it was hypothesized that the development of pancreatitis following ischaemia and reperfusion of the pancreas is a result of iNOS expression; the use of a selective iNOS inhibitor should then prevent the development of acute pancreatitis during reperfusion.

Materials and methods

Experimental animal model

Male Wistar rats weighing 249–333 g were randomly assigned to four experimental groups (*n* = 10 in each group). All animals were anaesthetized by intraperitoneal administration of 2·7 ml/kg of a mixture of one part midazolam 2 mg/ml (Hypnovel; Roche, Welwyn Garden City, UK), one part Hypnorm (fentanyl citrate 0·315 mg/ml plus fluanisone 10 mg/ml; Janssen, Saunderton, UK) plus two parts sterile water. Body temperature was maintained between 36·5 and 37·5°C by the use of a heating pad. Anaesthesia was maintained throughout the experiment by supplementary doses of the anaesthetic mixture given intramuscularly. The carotid artery was cannulated using an intravascular cannula (20G/32 mm; Portex, Hythe, UK) to allow continuous blood pressure monitoring (Lectromed, St Ouen, Jersey, Channel Islands) and the infusion of normal saline at 1 ml/h. In animals in groups 3 and 4, L-N^6-(1-iminoethyl)-lysine (L-NIL) (Alexis Corporation, San Diego, California, USA) was added to the infusion 1 h after the onset of reperfusion to provide a rate of administration of 6 mg per kg per h. All animals underwent laparotomy, whereupon the four main arteries supplying the pancreas (inferior pancreaticoduodenal, splenic, left gastric and gastroduodenal) were exposed microsurgically. Further intervention depended on the group to which the animal was assigned. In groups 1 (sham laparotomy) and 3 (L-NIL only), no further intervention was performed. In animals in group 2 (I–R only) and group 4 (I–R + L-NIL) the four main pancreatic arteries were occluded reversibly using microsurgical clips for 60 min. Ischaemia was confirmed by means of laser Doppler flowmetry (Moor Instruments, Axminster, UK). After 6 h of reperfusion in groups 2 and 4, and after an interval equivalent to the duration of ischaemia and reperfusion in groups 1 and 3, blood (0·5 ml) was withdrawn from the arterial cannula for subsequent measurement of serum α-amylase activity, and the pancreas was harvested and divided into three segments. The animals were then killed by an approved method without recovery from anaesthesia. All animal experiments were carried out in accordance with UK government legislation.

Outcome measures

Haematoxylin and eosin staining

One pancreatic segment was fixed in 10 per cent neutral buffered formalin, dehydrated by passage through a graded ethanol series, cleared in xylene and embedded in paraffin blocks. The blocks were cut into 4-μm sections and stained with haematoxylin and eosin, according to standard protocols. Sections were evaluated by light microscopic examination.

Pancreatic wet : dry weight ratio

The second segment of pancreas was blotted on paper and weighed; this represented the wet weight. The tissue was then placed in a vacuum oven at 60°C until a constant weight was obtained; this represented the dry weight. The pancreatic wet : dry weight ratio was then calculated for each animal.

Serum α-amylase activity

Sigma amylase reagent (Sigma, Poole, UK) was used for the quantitative kinetic determination of α-amylase in the serum.

Immunohistochemistry

The final pancreatic segment was fixed in 1 per cent paraformaldehyde in phosphate-buffered saline (PBS) for 4 h and then transferred into a storage buffer, PBS–sucrose, at 4°C until the cryostat blocks were prepared. Tissue sections (4 μm) were cut on a cryostat and applied to slides. The avidin–biotin complex immunoperoxidase staining system was used. The primary antibodies, anti-iNOS polyclonal and anti-eNOS polyclonal, were produced in rabbits and were obtained from Affiniti Research Products (Exeter, UK). The presence of positive staining with the specific antibody was indicated by the development of a reddish-brown stain, as a consequence of using the 3,3′-diaminobenzidine substrate. The presence or absence of staining and its cellular location was noted for each section, using both types of primary antibody in each group.

Statistical analysis

Continuous data are expressed as mean(s.e.m.). Data were analysed using analysis of variance with contrasts to define specific intergroup differences. Categorical (i.e. immunohistochemical) data were analysed using Fisher's exact test.

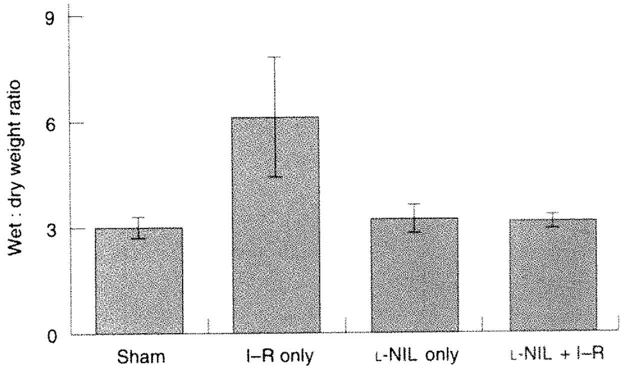
Results

Outcome measures

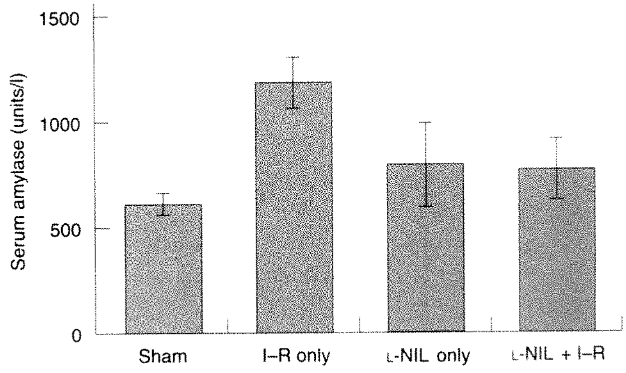
The diagnosis of acute pancreatitis was based on four criteria: macroscopic appearance of the pancreas, histological examination, an increase in pancreatic wet : dry weight ratio and a marked increase in serum amylase.

Macroscopic and microscopic appearance
The pancreas was enlarged, swollen and embedded in an oedematous gel in all animals subjected to I–R only, while it appeared relatively normal in all animals from the sham-operated groups (groups 1 and 3) and five animals in group 4 (I–R + L-NIL); the other five animals in the I–R + L-NIL group had only minimal macroscopic changes. Marked ascites and whitish areas of fat necrosis were present in eight animals who had I–R only. Pancreatic injury, as indicated by intracytoplasmic vacuoles, interstitial oedema and a polymorphonuclear cell infiltrate, was present only in samples from the I–R group (seven of ten animals). None of the samples from the other groups revealed histological evidence of pancreatic injury.

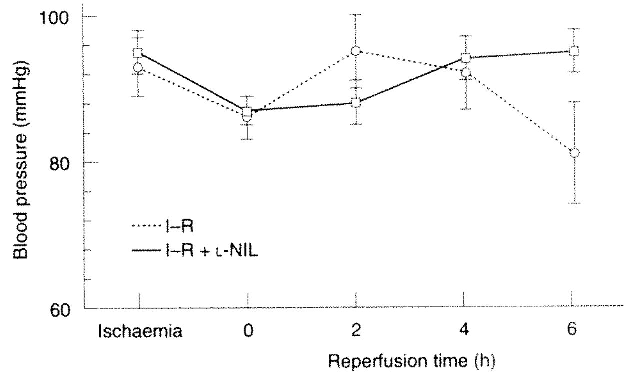
Pancreatic wet : dry weight ratio and serum amylase levels
Pancreatic wet : dry weight ratios (*Fig. 1a*) and serum amylase levels (*Fig. 1b*) were increased in the I–R group compared with values in the other three groups ($P < 0{\cdot}05$ for both outcome measures).



a Wet : dry weight ratio



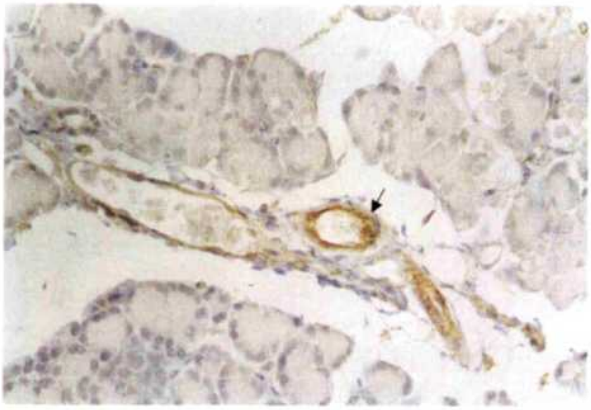
b Serum amylase



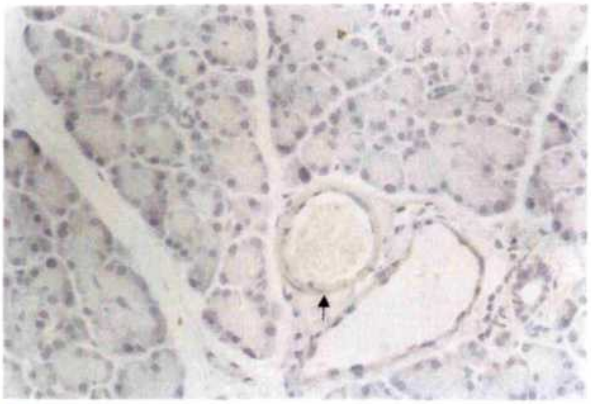
c Mean arterial blood pressure

Fig. 1 **a** Pancreatic wet : dry weight ratios, **b** serum amylase levels and **c** mean arterial blood pressure in rats subjected to sham operation or ischaemia–reperfusion (I–R) with or without L-N^6-(1-iminoethyl)-lysine (L-NIL). Values are mean(s.e.m.). Pancreatic wet : dry weight ratios and serum amylase levels were significantly increased, and blood pressure was significantly decreased, in rats subjected to I–R only compared with animals in all the other groups. Only groups that underwent I–R with or without L-NIL are shown in **c** for clarity

Arterial blood pressure
There was a reduction in mean arterial blood pressure at 6 h after the onset of reperfusion in animals subjected to I–R



a Ischaemia–reperfusion



b Ischaemia–reperfusion + L-NIL

Fig. 2 **a** Pancreatic section from rat subjected to 60 min of ischaemia and 6 h of reperfusion showing positive (reddish-brown) staining of the vascular smooth muscle and endothelium with anti-inducible nitric oxide synthase (iNOS) antibody (arrow). **b** In the presence of L-N^6-(1-iminoethyl)-lysine (L-NIL) there is no staining of the vascular smooth muscle and endothelium with anti-iNOS antibody (arrow). (Original magnification × 400)

only compared with all the other groups, which maintained a stable blood pressure throughout the experiment. At the end of the 6-h reperfusion period (*Fig. 1c*), mean arterial blood pressure was lower after I–R only than after I–R in the presence of L-NIL (79·0(6·1) *versus* 95(2·9) mmHg; $P < 0{\cdot}01$).

Immunohistochemistry

There was no staining with the anti-iNOS antibody in all specimens from group 1 (sham laparotomy), group 3 (L-NIL only) and group 4 (I–R + L-NIL); eight specimens from group 2 (I–R only) stained strongly positive for iNOS ($P < 0{\cdot}01$, Fisher's exact test). iNOS staining was mainly localized to the endothelium and vascular smooth muscle. *Fig. 2* shows the typical difference in iNOS staining between groups 2 and 4. Staining with the anti-eNOS antibody revealed pronounced and similar expression of eNOS within endothelial cells in all groups.

Discussion

In this study iNOS was expressed in pancreatic tissue following 60 min of total selective pancreatic ischaemia and 6 h of reperfusion, and this was associated with the development of acute pancreatitis as shown by macroscopic and microscopic appearance, doubling in wet : dry weight ratio compared with controls, and a serum amylase concentration above 1000 units/l. These changes were greatly attenuated by the administration of L-NIL, a relatively selective iNOS inhibitor, during the reperfusion period.

Although not previously reported in the pancreas, expression of iNOS following I–R has been described in a number of organs[4]. It remains debatable whether the increased production of nitric oxide resulting from this increased expression of iNOS is beneficial or detrimental to the tissues[4]. Two factors in experiments investigating the role of nitric oxide in I–R seem to account for these discrepancies: (1) a reperfusion period of less than 4 h (i.e. iNOS would not yet have been expressed) and (2) the use of non-selective NOS inhibitors, further impairing the already subnormal production of nitric oxide (as a result of low oxygen and NADPH concentrations, secondary to ischaemia) from eNOS in the very early reperfusion period. L-NIL, the NOS inhibitor used in the present study, exhibits a 30-fold selectivity for iNOS over eNOS and, more importantly, lacks inhibition of eNOS at the therapeutically useful dose employed here[8].

The literature regarding the role of nitric oxide in chemically induced pancreatitis is even more equivocal. Using *in vivo* microscopic techniques, Chen *et al.*[9] showed a positive correlation between the number of adherent leucocytes and pancreatic nitric oxide levels, while Inagaki *et al.*[10] showed that N^G-nitro-L-arginine (L-NA) increases the number of accumulated neutrophils. However, L-NA is a relatively selective inhibitor of eNOS and so would not inhibit nitric oxide production from iNOS. Two other studies showing that NOS inhibitors attenuate chemically induced pancreatitis have also used L-NA[11,12]. In addition, Dobosz *et al.*[13] have shown that L-arginine improves pancreatic perfusion, but aggravates the morphological changes.

Based on the findings of this study and recent reports that L-arginine attenuates pancreatic I–R injury during the early (less than 4 h) reperfusion period[5], it is very likely that nitric oxide plays a dual role in this situation. In the immediate reperfusion period, nitric oxide depletion results in a failure of the microcirculation, further aggravating the ischaemic insult[5]. Increased cytokine production, and possibly a depletion of nitric oxide itself, then activates the transcriptional nuclear factor κB leading to expression of iNOS[4]. This process will result in excessive nitric oxide production which appears to be detrimental to the pancreas, possibly as a result of its reaction with the superoxide anion to form the peroxynitrite radical. Under normal conditions, the constant removal of nitric oxide by haemoglobin and other reactions allows superoxide dismutase to reduce peroxynitrite formation by limiting the accumulation of superoxide anions. However, in the later stages of I–R, nitric oxide levels are vastly increased while the levels of antioxidants are decreased. Since nitric oxide has a greater affinity for the superoxide anion than superoxide dismutase, this leads to enhanced peroxynitrite formation[4]. In fact, the administration of superoxide dismutase has been shown to attenuate pancreatitis[3]. Peroxynitrite inhibits mitochondrial function and interacts with glutathione, rendering ischaemic tissue more susceptible to oxygen-derived free radical-mediated injury; it also inactivates tissue inhibitors of metalloproteinase, further enhancing proteolytic tissue destruction[4]. Excessive production of nitric oxide from iNOS has been implicated in the haemodynamic changes of acute pancreatitis[7]. Interestingly, in the present animal model of pancreatic I–R, mean arterial blood pressure decreased by 6 h of reperfusion, a time corresponding to the expected induction of iNOS, and this hypotension was prevented by administration of L-NIL.

In conclusion, it has been demonstrated that iNOS is expressed in the rat pancreas when subjected to an I–R insult, and that this process contributes to the development of pancreatitis. These findings suggest that the selective targeting of specific NOS isoforms may have important therapeutic applications; such an approach may be particularly apposite in the setting of pancreatic transplantation.

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Short note

Liver transplantation for early-detected, multifocal hepatocellular carcinoma

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Introduction

The indications for orthotopic liver transplantation (OLT) in patients with multifocal hepatocellular carcinoma (HCC) are controversial. Based on tumour node metastasis (TNM) staging[1], the results have been disappointing, with a 5-year survival rate for patients with T_3 or T_4 tumours ranging from 30 to 40 per cent. However, most series have been heterogeneous, with newly discovered multiple HCC being considered together with HCCs of long or unknown standing. In the authors' unit a policy of transplantation was adopted for all patients who developed multifocal HCC while on the waiting list.

Patients and methods

From 1990 to 1998 OLT was performed in 88 patients with recently discovered HCC (within 3 months or during evaluation for transplantation) superimposed on liver cirrhosis. Only patients with T_1 or T_2 stage disease at initial diagnosis were enrolled (T_1, solitary nodule of 2 cm or less in diameter; T_2, solitary nodule of 2 cm or less in diameter or monolobar multiple locations of 2 cm or less); patients with stage T_3 or T_4 lesions initially were excluded (T_3, monolobar multiple locations greater than 2 cm; T_4, multiple bilobar locations). Patients on the waiting list were followed by means of monthly abdominal ultrasonography. Extrahepatic tumour involvement or vascular invasion was considered an absolute contraindication. Evaluation of tumour stage and extrahepatic invasion was based on ultrasonography and computed tomography (CT), hepatic angiography and bone scan findings. The diagnosis of HCC was confirmed by histological examination of the native liver. Autopsy was performed in transplanted patients who died.

Values are given as mean(s.d.). Statistical analysis was performed with the Kaplan–Meier method and compared with the log rank test. The level of significance was considered as $P < 0\cdot05$.

Results

Table 1 shows the demographic and clinical characteristics of the patients. Sixty-four patients were positive for hepatitis C virus (HCV). An original TNM stage I or II progressed to III or IV in 13 patients during follow-up; examination of the native liver showed unrecognized T_3 and T_4 HCC in five patients.

Table 1 Demographic, clinical data and outcome of 88 patients with hepatocellular carcinoma

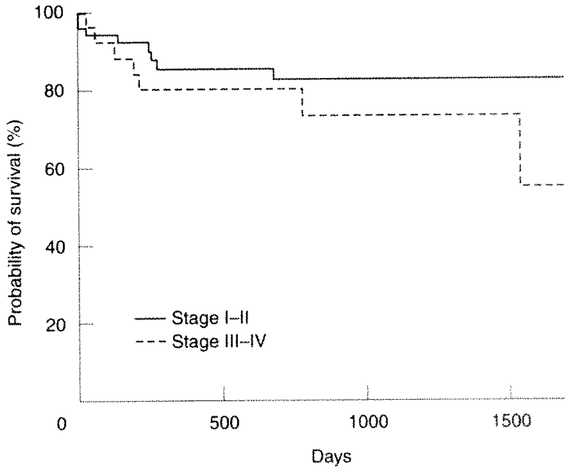
	UICC stage at time of OLT			
	Stage I (*n* = 26)	Stage II (*n* = 31)	Stage III (*n* = 7)	Stage IV (*n* = 24)
Age (years)*	52(7·7)	52(6·2)	52(6·0)	52(6·0)
Sex ratio (M : F)	18 : 8	25 : 6	7 : 0	21 : 3
Child–Pugh score of original cirrhosis				
A	7	10	2	8
B	10	11	2	14
C	9	10	3	2
Follow-up after OLT (days)*	845(568)	846(568)	854(586)	844(573)
Time from admission on to waiting list to OLT (days)*	97(93·4)	97(93·4)	61(34·0)	60(35·0)
Retransplantation†	1 vascular problem (day 8)	2 PNF (24 h) 2 DNF (days 10, 20) 1 biliary abscess (day 200) 1 vascular problem (day 31)	None	2 DNF (days 25, 44) 1 PNF (day 15)
Recurrence†	1 lung (day 878)	2 lung, graft (days 351, 1547)	1 graft (day 1429)	3 graft, lung, liver graft (days 169, 361, 1447)

*Values are mean(s.d.). †Number, cause or site, and time after OLT are indicated. OLT, orthotopic liver transplantation; PNF, primary non-function; DNF, delayed non-function; UICC, Union Internacional Contra la Cancrum

At transplantation, the TNM classification was stage I in 26 patients, stage II in 31, stage III in seven and stage IV in 24.

The mean(s.d.) interval from waiting list admission to transplantation was 97(93) days. The mean(s.d.) interval from recognition of stage III and IV lesions by ultrasonography at follow-up to transplantation was 60(35) and 61(34) days respectively. The mean follow-up interval after transplantation was similar for each tumour stage group.

For the purpose of survival analysis, patients with stage I and stage II lesions were grouped together, as were those with stage III and stage IV tumours. The adjusted 5-year survival rate after exclusion of early deaths unrelated to the original HCC (1 year) was 83 per cent for patients with stage I–II disease and 55 per cent for those with stage III–IV lesions (median(s.d.) follow-up 839(561) days; *P* not significant) (*Fig. 1*). *Table 1* shows the site of HCC recurrence (seven patients).



No. at risk				
Stage I–II	57	38	22	7
Stage III–IV	31	15	9	5

Fig. 1 Kaplan–Meier survival curves of patients with stage I and II *versus* stage III and IV disease classified according to Union Internacional Contra la Cancrum criteria

Discussion

The prognosis of patients who undergo liver transplantation for recently discovered, early stage, multifocal HCC is no different from that of patients with a single HCC and HCV cirrhosis without HCC. Transplantation was of benefit in patients with multiple tumour nodules who, by current TNM criteria, would have been excluded from surgery. This does not apply, however, to patients with multifocal tumours detected during random surveys of cirrhotic patients or to symptomatic patients, because these heterogeneous populations include those with tumours that have developed at different times with different prognoses depending on the case-mix of early *versus* late tumours[2].

The present results are comparable to those of Mazzaferro *et al.*[3] who reported 4- and 5-year survival rates of 75 and 74 per cent respectively after transplantation of early-stage multifocal HCC.

The key factors influencing the outcome of liver transplantation in multifocal HCC appear to be early diagnosis and timely operation.

Although the growth pattern of HCC is variable, these tumours are considered to grow slowly compared with other solid tumors[4]. Given that even the most rapidly growing HCC[5] would require 4·6 months to increase from the 1-cm limit of ultrasonographic detection to the critical size of 3 cm, a maximum interval of 4 months is a good compromise between the feasibility of transplantation and the likelihood of a recurrence-free outcome.

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Original article

Comparison of cardiac troponin I and creatine kinase ratios in the detection of myocardial injury after aortic surgery

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Background: Perioperative myocardial infarction may not be diagnosed correctly because World Health Organization criteria are often not met and creatinine kinase myocardial fraction (creatinine kinase/creatinine kinase MB isoenzyme; CK/CK-MB) ratios can be difficult to interpret. Cardiac troponin (cTn) I and cTnT are the most sensitive and specific markers of myocardial cell necrosis currently available but are not widely used in surgical practice. The aim was to compare cTnI and CK/CK-MB ratios in the detection of myocardial injury following aortic surgery.

Methods: This was a prospective study of 59 patients undergoing elective ($n = 28$) or ruptured ($n = 24$) abdominal aortic aneurysm repair or elective aortofemoral bypass ($n = 7$). cTnI level was measured before operation and at 6, 24 and 48 h after surgery. The CK/CK-MB ratio was measured where cTnI was detectable.

Results: Some 14 of 24 emergency and ten of 35 elective patients had detectable cTnI (greater than 0·5 ng/ml) at one or more time-points. The CK/CK-MB ratio was greater than 5 per cent in only four of 24 patients having an emergency operation and in none of the elective patients with detectable cTnI.

Conclusion: Over half of patients undergoing emergency operation and more than a quarter of those having elective aortic surgery suffered myocardial necrosis as determined by detectable cTnI levels. This was accompanied by a raised CK/CK-MB ratio in less than one-fifth of patients.

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Introduction

Perioperative myocardial infarction (MI) accounts for more than 50 per cent of all deaths occurring after emergency and elective aortic surgery[1–3]. Despite improvements in anaesthetic and surgical care, this value has remained unchanged. One obstacle to improving the outcome for such patients is the difficulty in making the diagnosis of MI in the early postoperative period. World Health Organization (WHO) guidelines for the diagnosis of MI require that two of the following three features are present: a history of characteristic prolonged ischaemic chest pain, evolutionary changes on the electrocardiogram (ECG) and/or an increase in serial cardiac enzyme levels[4]. However, symptoms are masked, atypical or absent in up 75 per cent of postoperative patients with objective evidence of myocardial ischaemia[5,6]. The ECG is often difficult to interpret[7,8] and does not display the classical changes of Q-wave infarction[9]. Creatinine kinase is released in large quantities from skeletal muscle as the result of direct surgical trauma and as a consequence of ischaemia and reperfusion injury[10–12]. This makes the creatinine kinase/creatinine kinase MB isoenzyme (CK/CK-MB) ratio difficult to interpret.

The troponins are normal muscle proteins involved in the calcium-regulated actin–myosin interactions[13]. Three subtypes exist. Troponin T binds to tropomyosin and attaches the troponin complex to the thin filament. Troponin I binds to actin and inhibits actin–myosin coupling. Troponin C binds to calcium and antagonizes the effect of troponin I[14]. Most troponin is tightly bound to this troponin complex, but about 6 per cent of troponin T and 2–3 per cent of troponin I is free in the cytoplasm[15].

Troponins I and T, but not C, exist as distinct cardiac-specific subtypes[16]. These structural, and therefore antigenic, differences have allowed the development of specific monoclonal antibodies to cardiac troponin (cTn) I and cTnT.

Improvements in the diagnosis of postoperative MI, allowing earlier detection and treatment as a result of troponin sampling, may improve morbidity and mortality. The aim of this study was to investigate the prevalence of cTnI release in patients undergoing elective and emergency aortic surgery and to examine the relationship between cTnI release and CK/CK-MB ratios.

Patients and methods

Patients

Fifty-nine patients were studied prospectively. There were 28 patients (26 men, two women) of median age 68 (range 54–81) years who had elective and 24 patients (22 men, two women) aged 74 (63–87) years who had emergency (for rupture) repair of an infrarenal abdominal aortic aneurysm (AAA). Seven patients (all men) aged 55 (49–68) years underwent elective aortofemoral bypass for occlusive disease. Ethics committee approval was gained, and either written informed consent was obtained from the patient or the study was discussed with the patient's next of kin until formal consent could be obtained.

Sample collection

Venous blood (9 ml) was collected into clot activator serum tubes before operation, and at 6, 24 and 48 h after surgery. The blood was allowed to clot over 30 min and then centrifuged at 2500 r.p.m. (1128g) for 15 min. Serum was removed and stored at −80°C for analysis in batches.

Operative methods

All operations were performed under general anaesthesia. Laparotomy was through a transverse supraumbilical incision in all cases. All elective patients had an epidural infusion of bupivacaine and diamorphine commenced before operation. No patient required suprarenal clamping. All elective patients received an intravenous bolus of 5000 units heparin before aortic clamping. Patients with a ruptured AAA did not receive systemic heparin.

Assay methods

Serum cardiac troponin I
Serum cTnI was measured by enzyme-linked immunosorbent assay (OPUS Troponin I; Dade Behring, Deerfield, Illinois, USA) using the fully automated OPUS II analyser (Dade Behring). The lower limit of detection of this assay is 0·5 ng/ml and a value equal to or greater than this level was considered positive for myocardial injury.

Serum creatine kinase/creatinine kinase MB isoenzyme ratio
Serum CK and CK-MB activities were measured by multiple-point rate assay (Vitros 700 CK and CK-MB slides; Johnson and Johnson, Rochester, New York, USA). The reference range for CK using this assay in men is 35–13 units/l and in women 55–170 units/l. The lower limit for detection of CK-MB was taken as 16 units/l. These values were then expressed as a percentage ratio of CK/CK-MB and, where this was greater than 5 per cent, the result was considered positive for myocardial injury.

Definitions of major postoperative cardiac events

Acute MI was defined using the WHO criteria that require two of the following three features to be present: ECG change, typical chest pain and cardiac enzyme rise[4]. Congestive cardiac failure was associated with chest radiographic evidence of pulmonary oedema; cardiac arrhythmias requiring therapeutic intervention; cardiac arrest or ventricular fibrillation and cardiac death.

Results

There were no perioperative deaths in the elective aortic surgery group. Ten of the 35 patients who had elective surgery had a cTnI rise during the first 48 h after operation (*Fig. 1*). None of these patients had a CK/CK-MB increase greater than 5 per cent. cTnI rise was associated with a clinically significant cardiac event in five of these patients. Of the remaining five patients with a cTnI rise, no cardiac

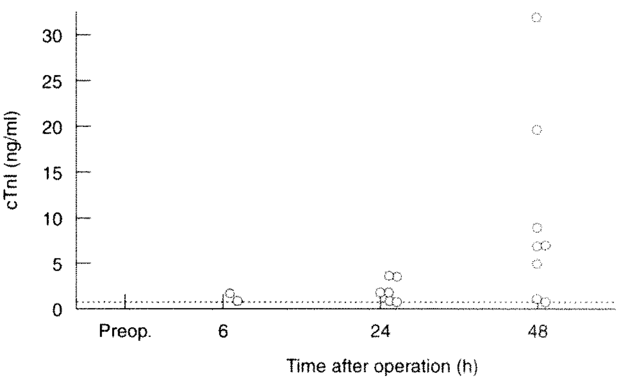

Fig. 1 Cardiac troponin I (cTnI) levels in the first 48 h after elective aortic surgery. Ten of the 35 patients had a cTnI level above the lower limit of detection (0·5 ng/ml), indicated by a dotted line

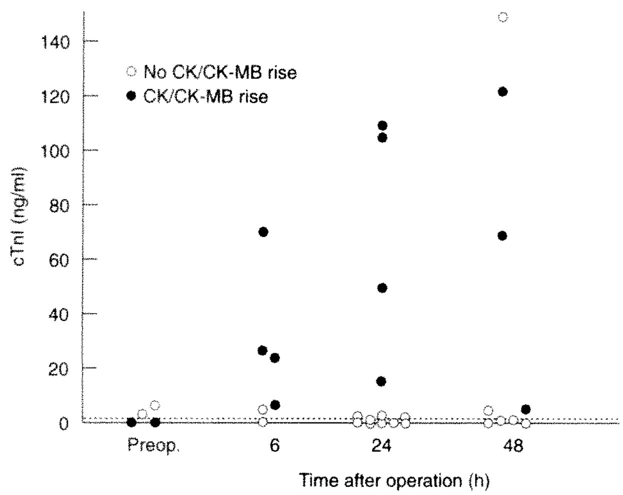

Fig. 2 Cardiac troponin I (cTnI) levels in the first 48 h after emergency aortic surgery. Fourteen of the 24 patients had a cTnI level above the lower limit of detection (0·5 ng/ml), indicated by a dotted line. cTnI levels in the four patients who had an increase in the ratio of creatinine kinase/creatinine kinase isoenzyme MB (CK/CK-MB) can also be seen

Table 1 Relationship between rises in cardiac troponin I level and creatinine kinase/creatinine kinase isoenzyme MB ratio in patients undergoing elective or emergency aortic surgery

	Cardiac troponin I	
CK/CK-MB	> 0·5 ng/ml	< 0·5 ng/ml
> 5 per cent		
Elective	0 (0)	0 (0)
Emergency	4 (3)	0 (0)
< 5 per cent		
Elective	10 (5)	26 (1)
Emergency	10 (6)	10 (1)

Values in parentheses denote the number of patients with a cardiac complication. CK/CK-MB, creatinine kinase/creatinine kinase isoenzyme MB ratio

event was identified. One other patient who had no perioperative cTnI rise had a clinically important cardiac arrhythmia that caused hypotension and required treatment.

Fourteen of the 24 patients who underwent emergency operation for ruptured AAA had a cTnI increase in the first 48 h after operation (*Fig. 2*). Of these, four had a CK/CK-MB rise greater than 5 per cent. cTnI increase was associated with a clinically significant cardiac event in nine patients. In the other five patients with a cTnI rise, no cardiac event was identified. One patient had a clinically important cardiac event in the absence of a cTnI rise. The relationship between cTnI, CK/CK-MB and clinical events is summarized in *Table 1*. Three patients with a cTnI rise died after operation as a result of cardiac arrhythmia and arrest. Five other patients with no cTnI rise also died: three suffered cardiac arrhythmia, one died from massive sepsis and one from pulmonary embolism.

Discussion

The principal finding of this study is that more than one-quarter of patients having elective operations and more than half of patients having emergency aortic surgery sustained myocardial injury as determined by a rise in cTnI concentration. In none of the elective patients and in only a quarter of the emergency patients was this associated with a diagnostic change in CK/CK-MB ratio. The use of the CK/CK-MB ratio alone will significantly under-diagnose myocardial injury in these patients and it cannot be recommended as a marker of cardiac damage in post-operative patients. The use of cardiac troponins in the detection of myocardial injury may be of value in this setting.

The question remains whether measurement of cTnI is oversensitive in the detection of myocardial injury, thus calling into doubt the significance of a rise in CK/CK-MB. A larger study would be required to answer this question. However, in the present study, a cTnI rise was associated with a clinically significant cardiac event in more than half of the cases. Furthermore, in most cases the cTnI rise predated any clinically apparent event. Previous work has suggested that a perioperative rise in cTnI concentration in general surgical patients is associated with poor outcome at 6 months and at 5 years[17,18]. A cTnT rise has also been associated with poor outcome in patients with sepsis[19]. Troponin-detected injury has been used to redefine 'unstable angina' as small MIs in some cardiac patients[20]. This is relevant in the perioperative patient as the majority of infarcts are of the non-Q wave type.

A rise in troponin signifies myocardial cell necrosis but gives no explanation as to the underlying mechanism of injury. In medical patients, chronic inflammation, infection, coagulation changes and catecholamine release have all been associated with the development of myocardial injury. These are certainly changes that will occur with aortic surgery. In addition, changes in blood pressure and myocardial perfusion pressure must all be considered as important in the pathogenesis of myocardial damage.

Even if myocardial injury could be diagnosed earlier and more accurately, it remains uncertain whether early therapy could affect outcome in terms of morbidity and mortality, either in the perioperative period or following discharge.

The finding of a cTnI rise appears to put a patient in a higher risk category for subsequent cardiac events. This knowledge might prompt changes in the invasive monitoring and the commencement of cardioprotective therapy. A variety of potential therapies exist, including beta-blockers, low molecular weight heparins, the antiplatelet glycoprotein IIb/IIIa receptor antagonists and even early coronary revascularization[21–26]. These treatments may have a similar important role in reducing morbidity and mortality rates from perioperative microinfarction; the early accurate diagnosis of myocardial damage with reliable cardiac markers, such as cTn, is therefore critical.

Acknowledgements

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Original article

Preservation of endothelial integrity and function in experimental vascular anastomosis with non-penetrating clips

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Background: Vascular repair with sutures is associated with disruption of the endothelial lining and subsequent thrombus formation on the intraluminal lesions. This experimental study was designed to determine whether the use of non-penetrating clips improved endothelial preservation.

Methods: In ten female pigs, 25-mm arteriotomies were made in both carotid arteries. The arteriotomies were repaired with jugular vein patches. On the left side, the repair was done with 1·4-mm titanium clips, and on the right side with two running 6/0 polypropylene sutures. Next, the aorta was divided and subsequently repaired with 2-mm clips in five of these pigs, and with two running 5/0 polypropylene sutures in the remaining five pigs. Endothelial function was studied at the anastomotic site in the carotid arteries by determination of endothelium-dependent and -independent relaxatory responses. Morphometric examination of the carotid arteries and inspection of the aortic endothelium were performed by means of scanning electron microscopy.

Results: Maximal endothelium-dependent relaxation to adenosine 5′-diphosphate was less in sutured than in clipped carotid arteries ($P < 0{\cdot}05$), while there was no difference in maximal endothelium-independent relaxation to sodium nitrite. This result in clipped carotid arteries was not accompanied by less intimal hyperplasia. Screening of the aortic anastomotic line showed better preservation of endothelial architecture after clip anastomosis. Mean cross-clamp time for carotid patch repair was significantly less when using clips than with sutures.

Conclusion: The use of non-penetrating clips for vascular anastomoses preserved endothelial function and structural integrity better than running sutures, although the degree of intimal hyperplasia was similar.

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Introduction

Currently, most vascular anastomoses are performed with surgical sutures attached to needles that penetrate the vessel wall, causing disruption of the endothelial lining. The sutures produce flow turbulence and form an inherently thrombogenic surface which serves as a nidus for the chronic build-up of fibrin. In addition, the needle-holes can leak and cause a haematoma. Intraluminal protruding sutures may predispose to stenosis at the anastomotic site with subsequent occlusion of the vessel[1–4].

A vascular anastomosis can also be performed using a VCS clip applier system® (AutoSuture, United States Surgical Corporation, Norwalk, Connecticut, USA). With this device, small titanium clips are applied in an interrupted fashion on 90° everted vessel walls; the clips do not penetrate the intima. The clips were designed for microvascular anastomoses and their use in small-calibre vessels has been reported by several authors[4–6]. The clips have also been used in large-diameter vessels. Although reports of long-term follow-up are lacking, its feasibility and the ease with which the device can be handled have been praised in both animal and clinical studies[6–9]. Unlike conventional suturing, a clipped vascular anastomosis may offer the advantage of a decreased cross-clamp time and a tight seal of the endothelium without the introduction of intraluminal foreign materials. This could improve endothelial function and integrity, possibly resulting in better patency rates[5,10,11]. A non-penetrating method of intimal approximation might improve patency rates; however, little is known about the effects of clips on endothelial function.

The aim of this study was to assess whether clip application contributes to improved endothelial function and integrity following vascular anastomosis. The use of clips and sutures was compared in medium-sized arteries in pigs, and morphological and functional changes were determined.

Materials and methods

Ten pigs were subjected to two different kinds of surgical intervention; in each, clips were compared with conventional running sutures. For evaluation of endothelial function, carotid arteriotomies were closed with a vein patch, on the left with clips and on the right with sutures. Arterial rings bearing the anastomoses were studied for endothelial responses in organ bath studies. For evaluation of endothelial integrity, transected aortas in consecutive experiments were closed alternately with clips or sutures, and analysed histologically by field emission scanning electron microscopy. Endothelial function and integrity were studied at 4 or 8 weeks after surgery, at which time five animals in each group were killed and the arterial specimens collected. The study was approved by the animal research ethics committee of the Faculty of Medical Sciences of the University of Groningen.

Surgical procedures

Ten female White pigs aged 10–12 weeks with a mean(s.e.m.) body-weight of 30·4(0·8) kg were used. The animals received water and food *ad libitum*. Animals were operated on under aseptic conditions and received antibiotic prophylaxis with ampicillin. Ketamine 20 mg/kg intramuscularly and diazepam 0·75 mg/kg intramuscularly were administered to anaesthetize the animals, after which intubation took place. Inhalation anaesthesia was accomplished with isoflurane (3–5 per cent during induction and 1·5 per cent for maintenance) and oxygen.

Through bilateral neck incisions, the jugular veins and carotid arteries were dissected from the surrounding tissues. Two patches were taken from the jugular vein with the larger diameter. Heparin (3000 units) was administered intravenously. A left carotid arteriotomy 25 mm in length was made. Four 6/0 polypropylene corner stitches were inserted to fix the patch and left in place as stay sutures. Edges of both the arteriotomy and the patch were everted to 90° by means of specially designed approximating forceps. The arteriotomy was then closed with the patch using clips (size M, 1·4 mm in diameter). Subsequently, on the right, a similar carotid arteriotomy (25 mm) was carried out and closed with a patch using two running 6/0 polypropylene sutures.

Next, the animal underwent a midline laparotomy. The infrarenal aorta was explored from the renal vein down to the aortic bifurcation. Two vascular clamps were placed and the aorta was transected at an angle of 45°. In five pigs the aorta was closed with two running polypropylene 5/0 sutures, while in the other five animals clips (size L, 2·0 mm in diameter) were used. After clamp release, patency was checked by clinical assessment and hand-held Doppler ultrasonography. The wounds were closed in layers. After operation no anticoagulant or antiplatelet medication was given.

Full-length carotid arteries and segments of the aortas containing the anastomoses were retrieved at the time of death, again under general anaesthesia.

Endothelial function study

The collected carotid arteries were placed in a buffer solution with the following composition: sodium chloride 120·4 mmol/l, potassium chloride 5·9 mmol/l, calcium chloride 2·5 mmol/l, magnesium chloride 1·2 mmol/l, sodium dihydrogen phosphate 1·2 mmol/l, sodium bicarbonate 25·0 mmol/l, glucose 11·5 mmol/l; continuously aerated with 95 per cent oxygen–5 per cent carbon dioxide. Indomethacin 10 μmol/l was added to the buffer solution to block the cyclo-oxygenase pathway in order to exclude the production of vasoactive endogenous prostaglandins.

Rings of 2 mm were cut from the vessel with a sharp razor blade after disposal of periadventitial tissue. From each carotid artery, four rings were taken at the site of the anastomosis. As controls, four rings were taken from at least 2 cm distal or proximal to the patch closure. The rings were mounted between two stirrups in organ baths containing the buffer solution at 37·5°C. One stirrup was anchored inside the organ bath and the other connected to a displacement transducer to determine isotonic changes, as described previously[12]. Rings were then subjected to 14 mN and allowed to equilibrate for 60 min, during which time regular washings were performed before the test itself was carried out. The rings were then primed and checked for viability by stimulation with 10 μmol/l phenylephrine and subsequent washings.

Phenylephrine 10 μmol/l was also used to induce a state of precontraction, and once a stable contraction level had been established endothelial-dependent (adenosine 5′-diphosphate (ADP) and bradykinin: 10 nmol/l to 100 μmol/l) and endothelial-independent (sodium nitrite: 10 μmol/l to 10 mmol/l) responses were determined, through cumulative administration of increasing doses of these different relaxatory substances. In preliminary experiments it was found that ADP and bradykinin, but not sodium nitrite, induced relaxation of pig carotid artery rings in the presence of indomethacin 10 µmol/l, which was virtually abolished by the additional presence of N^G-monomethyl-L-arginine 10 µmol/l (i.e. nitric oxide synthetase inhibition), which suggests that nitric oxide is the major mediator in these responses.

Vascular morphometry

For light microscopic examination, segments of the carotid anastomotic site were fixed by immersion in 10 per cent neutral buffered formalin. Clips were removed in the 'clipped' group and segments were embedded in paraffin. Sectioning took place perpendicular to the anastomotic line. Subsequently, 4-µm sections were cut and stained with haematoxylin and eosin, and with modified Verhoeff's elastic tissue stains.

The thickness of both the (neo)intima and media at the level of the patch repair, as well as in control rings, was quantified by videomorphometry. Intimal thickness was determined by scanning the intimal area from each ring through ten consecutive thickness measurements. Determination of medial thickness was done at the same level as the intimal scanning. Maximal and mean thicknesses of these vessel layers were calculated from each group of rings. Next, the area of the (neo)intima of the segments was measured, as well as the total area of all layers, and means were compared between the different groups of vascular rings. All readings were made by a single investigator in a blinded fashion.

Endothelial integrity study

Aortic specimens were analysed by means of field emission scanning electron microscopy. After resection, the aortas were rinsed with sodium cacodylate buffer 0·1 mol/l (pH 7·4), 6·8 per cent sucrose, 0·4 per cent sodium nitric oxide and heparin for 2 min, and subsequently prefixed by immersion in cacodylate-buffered 2 per cent glutaraldehyde (pH 7·4, 24 h, 4°C). The segments were then immersed in a mixture of arginine–hydrochloric acid, glycine, sucrose and sodium glutamite (2 per cent each) for 16 h at room temperature, and rinsed in distilled water three times. Next, the segments were immersed in a mixture of tannic acid and guanidine–hydrochloric acid (2 per cent each) for 8 h at room temperature, rinsed three times in distilled water and immersed for 8 h at room temperature in a 2 per cent osmium tetroxide solution in distilled water, as described previously[13]. Finally, the segments were dehydrated in ethanol and critical point dried in liquid carbon dioxide. All specimens were treated in the same way to prevent processing artefacts between the groups. Samples were investigated in a JEOL FEG SEM type 6301 F (Jeol USA, Peabody, Massachusetts, USA), operated at 2–5 kV, and screened for intraluminal penetration of sutures or clips, the presence of inflammatory cells, thrombus formation, exposure of subendothelial tissue, and endothelial damage and regeneration.

Statistical analysis

Data obtained from cross-sectional light microscopic specimens and cross-clamping times are expressed as mean(s.e.m.).

Maximal relaxation of the rings after administration of dilatory substances was derived from full dose–response curves. Student's paired or unpaired t test was used for statistical comparison of different groups. F analysis of variance was used for intraspecies comparison of the aortic specimen. $P < 0.05$ (two tailed) was considered statistically significant.

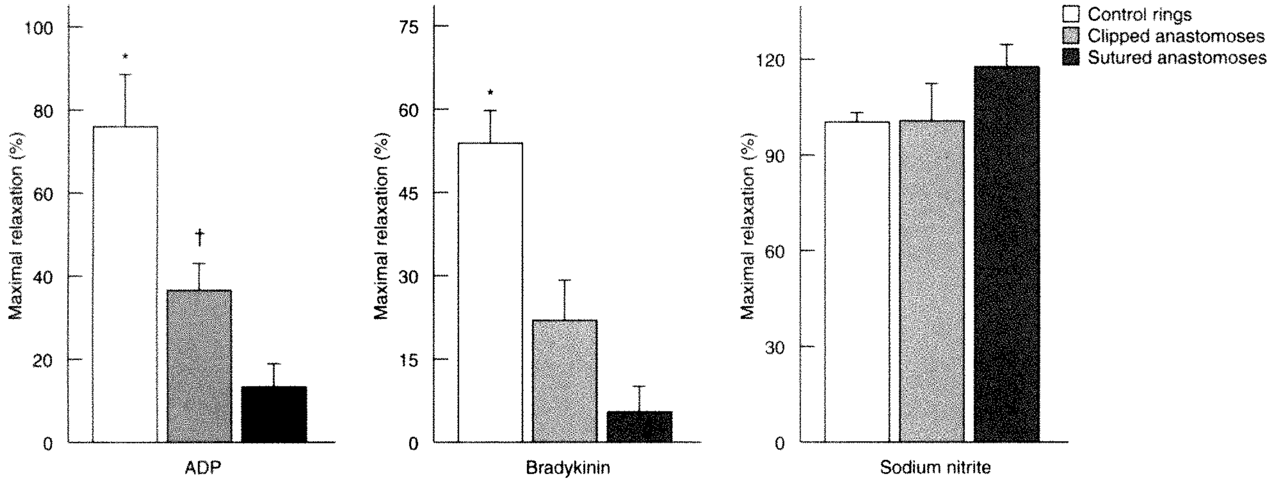
Results

All animals survived the procedure without postoperative complications. In particular, no signs of minor or major stroke were seen. The results for animals that were killed after 4 weeks and those killed after 8 weeks were taken together after determination that there were no significant differences between these groups with respect to the quantitative outcome variables.

Duration of anastomosis

The mean cross-clamping time was defined as the time to place the vascular clamps, perform the arteriotomy, place stay sutures in the 'clipped' group and complete the anastomosis. For the carotid anastomoses, the mean(s.e.m.) cross-clamping time for sutures was 19·9(0·8) min. With clips, the time was significantly reduced to 13·5(0·6) min ($P < 0.001$, paired t test). A trend towards reduction in mean cross-clamping time was also observed for the clipped aortic anastomoses, but the difference was not statistically significant (16·2(1·5) min using sutures *versus* 12·8(1·2) min with clips).

All 30 anastomoses (20 carotid arteries and ten aortas) remained patent until death. No salvage procedures were carried out. At death, none of the animals suffered signs of leakage, infection or anastomotic aneurysm. No clip was dislodged.



a ADP **b** Bradykinin **c** Sodium nitrate

Fig. 1 Maximal relaxation to **a** adenosine 5′-diphosphate (ADP), **b** bradykinin and **c** sodium nitrite of pig carotid artery rings bearing either clipped or sutured anastomoses; 'extra-anastomotic' rings were used as a control. Relaxation is expressed as a percentage of phenylephrine-induced precontraction. Values are mean(s.e.m.). *$P < 0·01$ control *versus* clipped and sutured anastomoses, †$P < 0·05$ clipped *versus* sutured anastomoses (Student's t test)

Endothelial function

Maximal endothelial-dependent and -independent responses of carotid rings are shown in *Fig. 1*. Maximal relaxation to ADP and bradykinin (*Fig. 1*) was significantly reduced in carotid rings bearing the anastomoses (i.e. irrespective of technique) compared with control rings, thus indicating that anastomoses *per se* attenuated endothelium-dependent relaxation. In the anastomotic vascular rings, maximal relaxation in response to ADP was 2·7-fold less ($P = 0·024$) and that to bradykinin was 2·8-fold less (P not significant) after suturing than clipping. This indicated that endothelium-dependent relaxation was better preserved by clipping than by suturing. The maximal relaxation with sodium nitrite remained similar in anastomotic rings and controls. Also, there was no significant difference in response to sodium nitrite between the clipped and sutured anastomoses (*Fig. 1*). This indicated that the above differences in endothelium-dependent relaxation could not be explained by alterations in vascular smooth muscle cell responsiveness to nitric oxide.

Vascular morphometry

Cross-sectional morphological examination of the carotid rings showed marked thickening of the vessel wall, which was macroscopically visible at the site of the venous patch. In contrast, control rings showed no thickening. Mean thicknesses of both the intima and media in anastomosed vessels are presented in *Fig. 2a*. All anastomoses showed mild to moderate signs of intimal hyperplasia, regardless of the method of closure (*Fig. 3*). Measurements of mean(s.e.m.) maximal intimal thickness of the rings showed the same pattern as the 'mean thickness' findings: 1447(83) μm with clips and 1145(60) μm with sutures ($P = 0·01$).

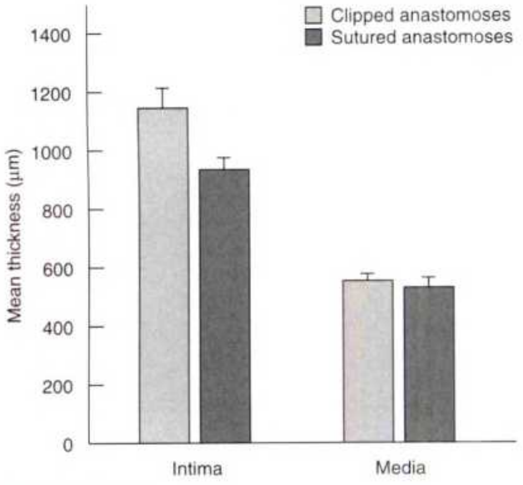
Inspection of the medial layer showed no significant difference in mean thickness between the clipped and sutured vessels (*Fig. 2*). The same applied to mean(s.e.m.) maximal medial thickness, which was 689(31) μm with clips, 642(37) μm with sutures ($P = 0·36$) and 556(27) μm in control rings.

Mean total cross-sectional area measurements are shown in *Fig. 2b*. Compared with control rings, both anastomotic techniques produced a significantly increased degree of intimal hyperplasia. There were no differences in degree of intimal hyperplasia determined by area measurements between the two techniques.

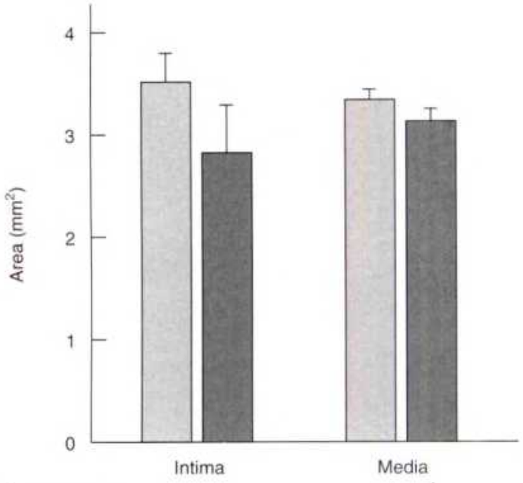
The mean proportion of intimal hyperplasia expressed as a percentage of the total area was 50·1 per cent in clipped anastomoses and 45·3 per cent in sutured anastomoses ($P = 0·22$).

Endothelial integrity

Inspection of the aortic endothelium at the sutured anastomotic line after 4 weeks using scanning electron microscopy showed a rough surface with parts of suture material protruding intraluminally. In contrast, inspection

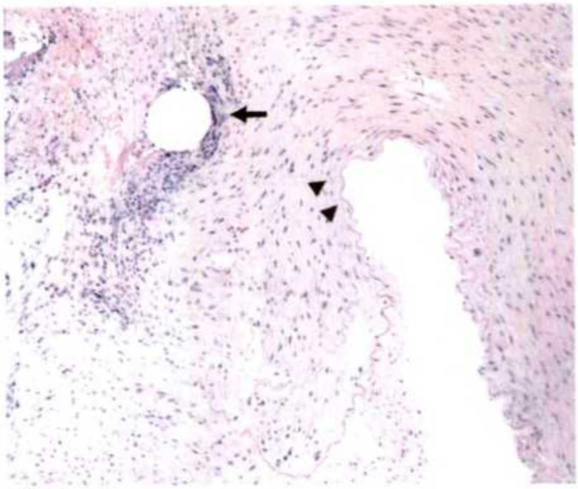


a Thickness

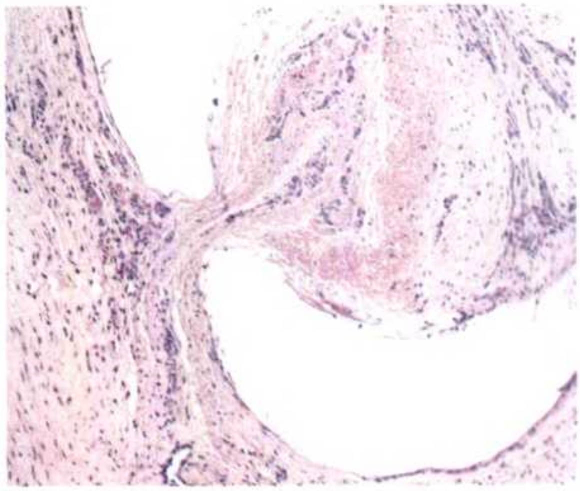


b Area

Fig. 2 Quantitative measurements of intimal hyperplasia and medial hypertrophy by videomorphometric determination of **a** mean thickness of intima and media, and **b** mean total area of both vessel layers. Values are mean(s.e.m.). $^*P < 0.05$ clipped *versus* sutured anastomoses (Student's *t* test)



a Sutured



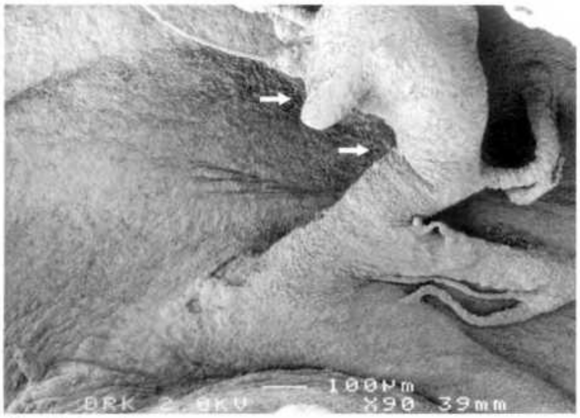
b Clipped

Fig. 3 Haematoxylin and eosin-stained histological specimen of carotid artery vein patch closure with **a** sutures (luminal site indicated by arrowheads and empty area of removed suture by an arrow) and **b** clips. In **b,** note the empty arcuate-shaped area of the removed clip. (Original magnification × 25)

of clipped anastomotic sites revealed a smooth surface and a tightly sealed endothelial layer without clips protruding into the lumen (*Fig. 4*). Inspection of sutured anastomotic sites in greater detail showed endothelial cells that were irregular in size and shape. At the sutured anastomotic sites there was fibrin deposition, thrombi and a more pronounced inflammatory reaction (increased lymphocytes and white blood cells), which were localized at the insertion of the suture. At the clipped anastomotic sites the endothelial cells were uniform in size and shape, and closely apposed to one another. Fibrin, platelets and white blood cells were rarely seen (*Fig. 5*). After 8 weeks the amount of thrombi and inflammatory cells at sutured anastomotic sites had decreased compared with the appearance at 4 weeks. Some of the sutures were still not completely covered by neoendothelium. The endothelial surface at the clipped anastomotic sites remained regular and smooth. None of the clips had migrated into the lumen.

Discussion

In this experimental study, after conventional sutured anastomosis there was incomplete endothelial coverage,



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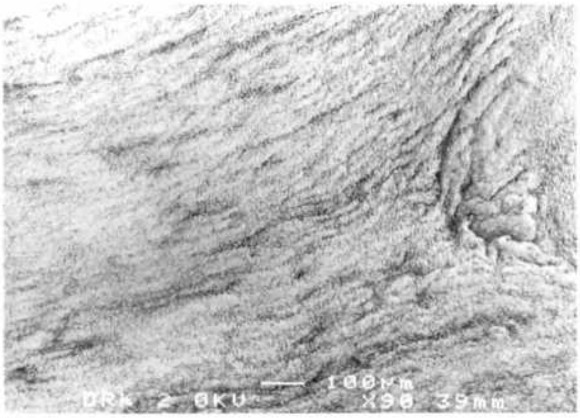
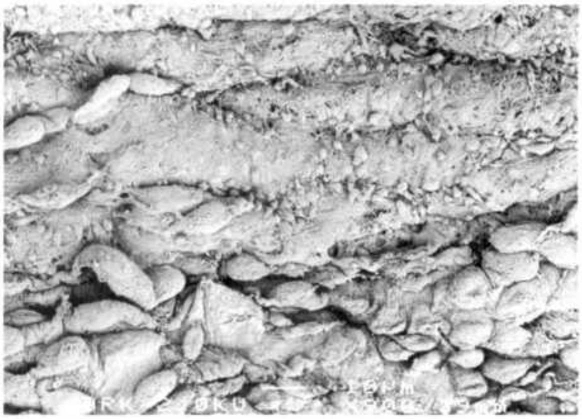


b Clipped

Fig. 4 **a** Sutured aortic anastomosis 4 weeks after operation. Scanning electron microscopy at the anastomotic line shows parts of sutures, covered with neoendothelium and protruding intraluminally, indicated by arrows. **b** At the anastomotic line of a clipped anastomosis none of the clips compromises the intima or causes endothelial disruption. Endothelial cells form a continuous and homogeneous layer. (Original magnification × 90)



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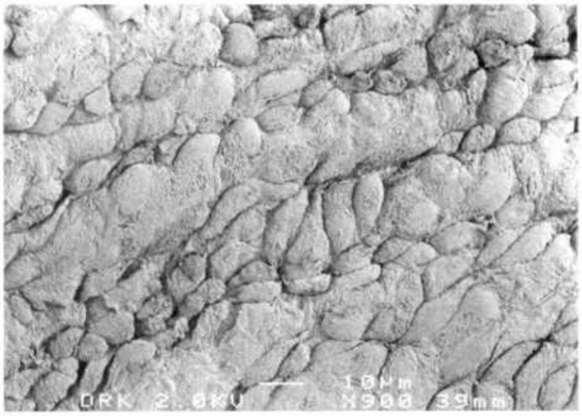

b Clipped

Fig. 5 **a** Detailed scanning of the aortic anastomosis shows recruitment of inflammatory cells along the sutured endothelial surface. Endothelial cells were irregular in size and shape compared with those in clipped anastomosis. **b** Endothelial cells at the site of a clipped aortic anastomosis are uniform in size and shape. (Original magnification × 900)

leaving the highly thrombogenic subendothelial matrix exposed to the bloodstream. Extensive fibrin and platelet deposition was seen on the endothelial surface at the anastomotic site of the aortic specimens. All of these phenomena were less prevalent or even absent when clips were used. A clipped anastomosis may be less thrombogenic. These findings regarding endothelial integrity are consistent with the scanning electron microscopy findings of others[2,14,15].

There was a significant reduction in maximal endothelium-dependent relaxation in response to ADP, as well as to bradykinin, of all anastomotic rings irrespective of the technique in comparison with control rings. In addition, maximal relaxation of anastomotic rings to ADP was better preserved by clip anastomosis than by sutures. Similar results were observed with bradykinin, although in this series of experiments the variation was too large for statistical significance. All the differences in endothelial responses were consistent with the findings obtained with scanning electron microscopy of aortic specimens, as mentioned above.

These findings are supported by the results of a study conducted by Lisi *et al.*[16], in which endothelial responses of vessels repaired with VCS microclips were compared with 8/0 polypropylene sutures. There was a modest, but significant, reduction in maximal relaxation of anastomotic rings compared with control rings, but no significant differences between clipped and sutured anastomoses. In the present study, the decrease in maximal relaxation of the anastomosis was greater (three- and fivefold decreases for

ADP and bradykinin respectively) compared with the decrease noted by Lisi *et al.*[16], whose experiments were done immediately after the anastomosis and reflect acute effects. The present data and data from the literature[16] suggest that anastomoses *per se* cause a moderate initial loss in endothelial function, which progresses over time, and that this progressive loss in endothelial function and integrity is more pronounced after sutured than clipped anastomosis.

The bradykinin- and ADP-induced relaxations in the presence of indomethacin in the present study reflect the capacity of the endothelium to produce and release nitric oxide after receptor stimulation. Nitric oxide stimulates guanylate cyclase to increase guanosine 3′,5′-cyclic monophosphate levels, not only in smooth muscle cells to cause vasodilatation, but also in platelets to cause inhibition of aggregation and of adhesion to endothelial cells[12,17–19].

Intact endothelial function has a protective role in preventing vasospasm and thrombus formation. Impaired endothelial function can lead to intimal hyperplasia[20,21]. Many authors have suggested that clips might reduce the formation of intimal hyperplasia compared with sutures, but quantitative measurements have not confirmed this[11,22–25]. In the present study there was significantly more intimal thickening after clipped than after sutured carotid anastomosis, but area measurement of the degree of intimal hyperplasia was similar. Therefore, the preservation of endothelial integrity with clips could not be explained by a reduction in intimal hyperplasia. It might, however, be explained by the fact that a continuous (suture) was compared with a discontinuous (clip) technique. An interrupted, everted anastomosis is more compliant than a continuous running-suture anastomosis[26]. Studies in which interrupted sutures are compared with clips have been conducted only in microsurgical anastomoses so far. Patch closure of a medium-sized vessel such as the carotid artery would not be done with interrupted sutures in a clinical setting because of prolonged clamping times and the risk of subsequent cerebral ischaemia.

An important limitation of the clinical use of clips may be the presence of plaques and atheroma in thick-walled arteries of vascular patients, which differ from the thin-walled arteries of a normal pig. In this situation proper coaptation of the vessel walls without bleeding is tedious and may restrain the surgeon from using clips[27].

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Original article

Preserved endothelial integrity and nitric oxide synthase in saphenous vein grafts harvested by a 'no-touch' technique

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Background: The saphenous vein is the most commonly used conduit for coronary artery bypass surgery, but 1-year occlusion rates as high as 30 per cent have been reported. In conventional surgery, considerable damage to the vein occurs during harvesting. The aim of this study was to compare endothelial integrity and nitric oxide synthase (NOS) in saphenous veins harvested by a novel 'no-touch' technique and veins harvested conventionally.

Methods: Immunohistochemistry was used to study endothelial integrity, and a combination of histochemistry and autoradiography was employed to identify NOS in human saphenous veins harvested by conventional and no-touch techniques.

Results: The endothelial lining of conventional grafts was reduced compared with that of no-touch grafts (52 *versus* 73 per cent; $P = 0.04$). This was associated with a concomitant reduction of NOS availability; NOS was also present in the adventitial vasa vasorum of no-touch vessels.

Conclusion: Some of the sites with potential for nitric oxide release *in vivo* are removed during conventional saphenous vein harvesting. These sites were preserved after no-touch harvesting, suggesting the potential to improve coronary artery bypass graft patency.

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Introduction

Autologous saphenous vein is the most commonly used conduit for surgical revascularization procedures. Occlusion rates for grafts in both infrainguinal bypass procedures and coronary artery bypass grafting (CABG) are relatively high: up to 15–30 per cent during the first year and approximately 50 per cent within 10 years[1, 2]. Factors contributing to graft failure include adventitial and endothelial damage that results in vasomotor dysfunction and vascular remodelling[3].

Conventionally, during harvesting of the saphenous vein, the perivascular tissue is stripped from the vein and venospasm encountered during vein harvest is overcome by vein distension. These procedures result in significant denudation of the luminal endothelium[4]. In an effort to reduce vasospasm, various methods have been employed, including vasodilators such as papaverine[5] and glyeryl trinitrate–verapamil solution[6]. These reduce the distension pressure required to overcome venospasm, although no clear advantage to graft outcome has been reported. Various atraumatic techniques have been described to reduce vein damage during harvest, such as a 'no-touch' technique introduced over 20 years ago[7]. These techniques avoid high-pressure distension, but mechanical distension is still generally used[8].

Recently, a new surgical technique has been described in which the saphenous vein is harvested together with a cushion of surrounding tissue, with minimal handling of the vessel[9]. This technique avoids venospasm, thus eliminating the need for distension. An angiographic follow-up study of 52 patients showed that 118 of 124 vein grafts prepared by this technique during CABG remained patent at 18 months, a significant improvement on vessels harvested conventionally[10]. The mechanisms underlying these results are unclear, although scanning electron microscopy has indicated that there is improved endothelial integrity in grafts harvested by this technique[11].

Nitric oxide is synthesized from L-arginine by the vascular endothelium by the enzyme nitric oxide synthase (NOS). Nitric oxide mediates vasodilatation and plays a key role in the maintenance of vascular tone[12]. It also has an inhibitory effect on platelet aggregation and adhesion, thereby exerting a thromboresistant action[13].

Endothelial injury results in impaired nitric oxide release by endothelial cells, and reduced nitric oxide activity has been observed in experimental models of saphenous vein grafting[14]. The preservation of endothelial integrity in vein grafts may improve graft patency rates by preserving nitric oxide activity.

This study compared endothelial integrity and NOS distribution of saphenous vein grafts harvested by the no-touch technique with those harvested by the conventional technique.

Patients and methods

Surgery and tissue preparation

Local ethics committee approval and informed consent from patients were obtained. Saphenous vein was harvested from ten consecutive patients undergoing CABG at the Orebro Medical Centre Hospital in Sweden; each patient received at least two vein grafts. The proximal segment of the saphenous vein was harvested with its surrounding tissue using the no-touch technique described previously[9] (*Fig. 1*), whereas the distal part was stripped of its surrounding tissue and adventitia, and distended with saline at a pressure of 300 mmHg for 1 min using a syringe connected to a manometer (*Fig. 1*). Both segments were stored until use in heparinized blood obtained from the arterial cannula of the cardiopulmonary bypass. Samples of excess vein graft were then taken from the two vein segments on completion of the proximal anastomosis. Tissue was frozen within 10 min and stored at – 70°C.

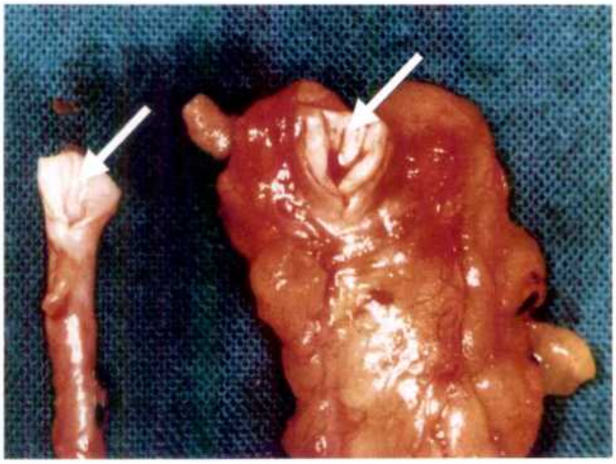


Fig. 1 Long saphenous vein grafts removed by conventional (left) and no-touch (right) techniques. Arrows indicate the lumen of the vein graft

Transverse sections of 10 μm were cut in a cryostat at approximately – 25°C, and three sections from each vein segment were sequentially thaw-mounted on to ten polylysine-coated microscope slides. The slides were coded so that vein segments could be analysed blind, stored at – 70°C, and transferred on carbon dioxide pellets to the Royal Free Hospital, London, for subsequent processing.

Immunohistochemistry

Immunohistochemistry was performed using the avidin–biotin complex (ABC) method. Briefly, sections were allowed to equilibrate at room temperature for 30 min. They were then fixed in acetone for 20 min at – 20°C and rinsed in phosphate-buffered saline (PBS) 0·01 mol/l. Endogenous enzyme activity was inhibited by preincubating sections in 0·5 per cent hydrogen peroxide in methanol for 10 min. Sections were then incubated in 5 per cent normal goat serum in PBS at room temperature for 20 min to block background staining. The tissue was incubated in either CD31 (1 : 2000 dilution; Dako, Glostrup, Denmark) to identify endothelial cells or collagen IV mouse monoclonal antibody (1 : 100 dilution; Dako) to identify collagen, for 60 min at room temperature. After incubation, sections were rinsed with PBS and incubated with biotinylated secondary goat antibody for 30 min. After further rinses, sections were incubated with streptavidin-biotinylated horseradish peroxidase solution for 30 min (StreptABCComplex/HRP duet, Mouse/Rabbit kit; Dako). 3,3′-diaminobenzidine tetrahydrochloride was used as the chromogenic substrate solution. Sections were counterstained with Mayer's haematoxylin and prepared for microscopic examination.

Autoradiography

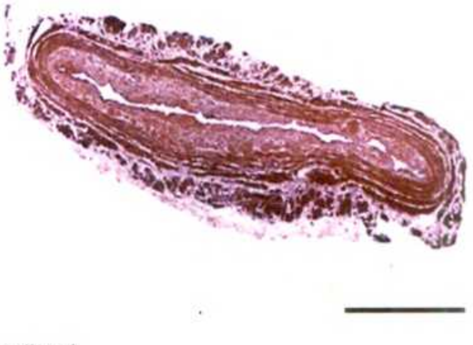
In vitro autoradiography was used to study NOS sites using [^{3}H]L-N^G-nitroarginine (NOARG)[15]. Slides were brought to room temperature and preincubated in Tris-hydrochloric acid buffer 50 mmol/l, pH 7·2, at room temperature for 30 min. Slides were then transferred to buffer (plus calcium chloride 5 mmol/l) containing NOARG 10 nmol/l (specific activity 55 Ci/mmol; Amersham Pharmacia Biotech, Little Chalfont, UK) and incubated for 1 h. The degree of non-specific binding was determined by incubating adjacent sections in the presence of an excess concentration (10 μmol/l) of unlabelled L-arginine (Sigma-Aldrich®, Poole, UK). After incubation slides were washed three times for 2 min in Tris buffer (4°C), dipped in distilled water (4°C) and dried in a stream of cold air. Sections were allowed to dry overnight at room temperature and were then postfixed in paraformaldehyde vapour for 2 h at 80°C. Slides were then dipped under darkroom conditions in molten K2 nuclear emulsion (Ilford, Mobberley, UK) and allowed to dry overnight. They were then placed in racks in lightproof boxes containing desiccator. These were sealed and stored at 4°C for 12 weeks, after which the emulsion was processed according to the manufacturer's instructions. Tissue was then stained with Mayer's haematoxylin and eosin for histological examination, viewed under dark-field and bright-field illumination on an Olympus BX50® microscope (Olympus Optical, London, UK) and photographed where appropriate.

Reduced nicotinamide adenine dinucleotide phosphate–diaphorase histochemistry

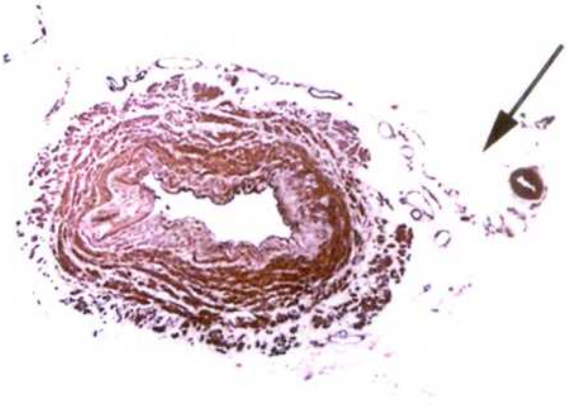
Localization of putative nitric oxide-producing cells was also performed by identifying NOS using reduced nicotinamide adenine dinucleotide phosphate (NADPH)–diaphorase histochemistry, as described previously[16]. Slide-mounted sections were allowed to equilibrate at room temperature (approximately 22°C) for 30 min before being fixed for 30 min in 3 per cent paraformaldehyde in 0·01 mol/l PBS buffer at 4°C. After rinsing in PBS and drying in cold air, sections were incubated for 1 h at 37°C with NADPH 1 mg/ml and nitroblue tetrazolium 0·1 mg/ml dissolved in PBS buffer (pH 7·6), containing 0·2 per cent Triton X-100. The incubation solution was then removed and the sections were blotted and rinsed for 5 min in running tap water. Sections were then stained for 3 min with 0·1 per cent eosin and prepared for microscopic examination. Controls were incubated with nitroblue tetrazolium and no NADPH.

Quantitative assessment of endothelium

Quantitative assessment of CD31 staining on vessel sections was carried out using a Kontron Zeiss 400 imaging system (Karl Zeiss Imaging, Cambridge, UK). This was performed on vessels from all ten patients; three sections per vein segment were used. The amount of positive luminal immunostaining was measured with a Polaroid CCD camera (Photonic Science, Cambridge, UK) attached to a Nikon E800 microscope (Nikon UK, Kingston upon Thames, UK) at × 4 magnification. The perimeter of the lumen was measured, and endothelial integrity (positive CD31 staining) was expressed as a percentage of the lumen length.



a Conventional



b No-touch

Fig. 2 Collagen content of long saphenous vein grafts. Transverse sections of saphenous vein harvested by **a** conventional and **b** no-touch techniques, stained with anticollagen IV mouse monoclonal antibody. Note the pronounced staining of the adventitia in no-touch tissue (absent in the conventional segment) with its abundance of microvessels (arrowed). Scale bar, 250 µm

Statistical analysis

Results are presented as median (range). Statistical analysis was performed with a two-tailed Wilcoxon signed rank test. $P < 0·05$ was considered statistically significant.

Results

Patient demographics

The mean age of the ten patients was 66 (range 57–81) years. There were two women; three patients were smokers and two were diabetic. All the patients were taking aspirin, nine were on beta-blockers and antihypertensives, and eight were receiving lipid-lowering medication.

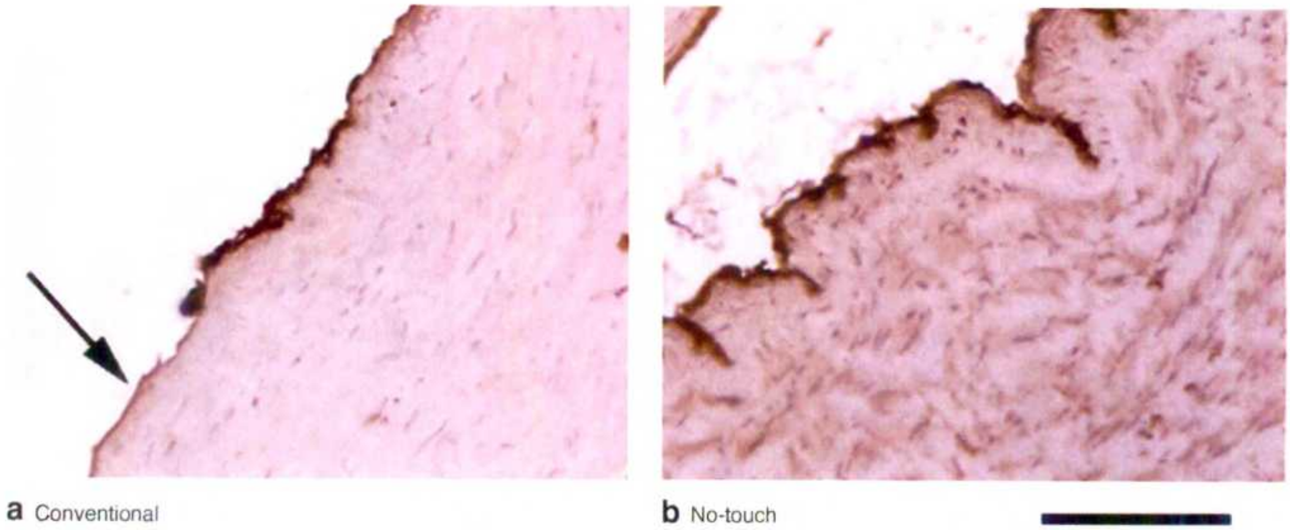

a Conventional **b** No-touch

Fig. 3 Luminal endothelium of vein grafts harvested by **a** conventional and **b** no-touch techniques. Endothelial cells were identified with CD31 with positive brown staining. Note the endothelial denudation of part of the conventional section (arrowed). Staining of the lumen of the no-touch section was almost continuous. Sections were used for the estimation of luminal endothelium shown in *Table 1*. Scale bar, 100 μm

Collagen

Collagen immunostaining showed the intact adventitia surrounding vessels harvested using the no-touch technique and revealed microvessels within this area. This cushion of tissue was absent in segments of saphenous vein that had been prepared using the conventional method, where the adventitia and surrounding paravascular tissue was removed (*Fig. 2*).

Table 1 Endothelial integrity of vein graft sections following conventional and no-touch harvest in ten patients

Endothelial integrity	Conventional harvest	No-touch harvest
Luminal CD31 staining (%)		
Median (range)	52 (30–90)	73 (56–93)*
95 per cent confidence interval	43–71	65–82

*$P = 0.04$ *versus* conventional harvest (Wilcoxon signed rank test)

Endothelium

The CD31 immunostaining (identifying endothelial cells) showed that the endothelial cell integrity of the no-touch vessels was well preserved (73 per cent), whereas in conventionally harvested veins it was reduced (52 per cent) (*Table 1*; *Fig. 3*). In the no-touch segments, positive CD31 immunostaining was often evident as 'folds' within the vessel lumen, whereas staining in conventionally harvested vessel segments was patchy but unfolded due to saline distension. Immunostaining was also evident in the endothelial cells of the vasa vasorum within the adventitia in segments of 'no-touch' saphenous vein.

Autoradiographic localization of nitric oxide synthase

NOS was identified on sections by incubating tissue in buffer containing NOARG. There was endothelium-dependent radioligand binding on the luminal aspect of vessels, which was almost continuous in saphenous vein removed with the no-touch technique but reduced on the conventionally prepared segments (*Fig. 4*). There was also weak medial binding and patches of binding within the adventitia (not shown).

Reduced nicotinamide adenine dinucleotide phosphate–diaphorase histochemistry

In sections from all vessel segments the pattern of luminal NADPH–diaphorase staining was similar to that of CD31 immunoreactivity and NOARG binding. These observations suggest that NADPH–diaphorase was identifying endothelial NOS. NADPH–diaphorase staining of no-touch harvested vein was almost continuous and folded on the luminal aspect of the veins, compared with poor staining

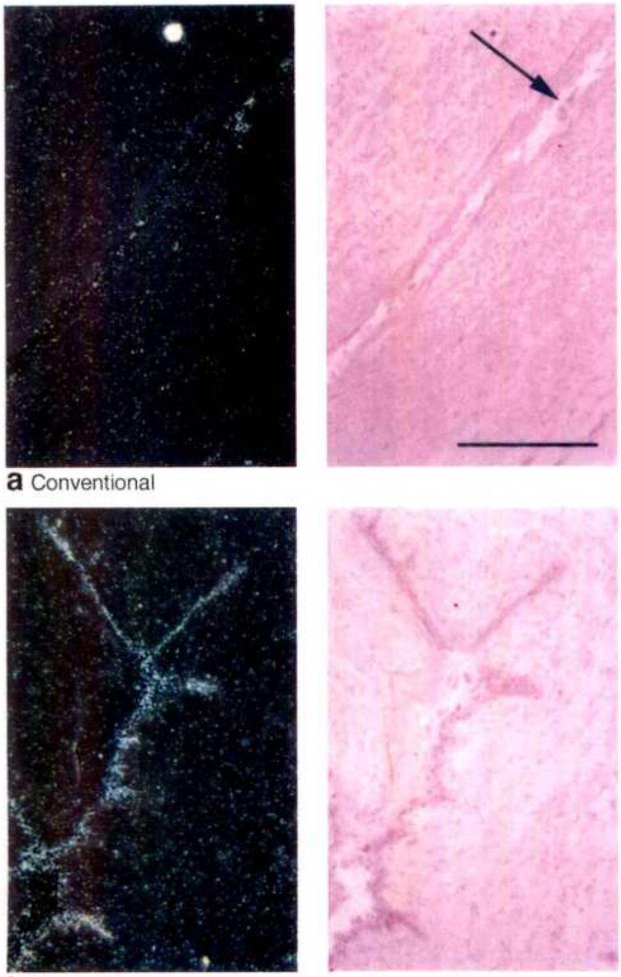


Fig. 4 $[^3H]$L-N^G-nitroarginine binding to **a** conventionally harvested and **b** no-touch vein grafts. Nitric oxide synthase was identified by *in vitro* autoradiography. Binding is shown on the left-hand panels under dark-field illumination, as white grains on a black background. The panels on the right are haematoxylin and eosin-stained tissue underlying the autoradiographs. The endothelium is continuous on no-touch sections (**b**), whereas only a few endothelial cells remain in the conventional segment

in conventionally harvested veins. NADPH–diaphorase staining was also observed in the intact adventitia of the no-touch vessels (*Fig. 5*) and was associated with the endothelium (positive CD31 staining) of the vasa vasorum.

Discussion

One of the major factors associated with vein graft failure is thought to result from adaptation of the vein to arterial conditions (increased pressure, shear and pulsatile motion). Here, endothelium-derived factors, such as nitric oxide, play a role by influencing vascular smooth muscle cell proliferation and migration. Removal of the adventitia (as occurs in conventional vein harvesting) reduces the tissue mass of the graft vein, making it more prone to distension, endothelial damage and subsequent graft failure. Recent evidence, in a porcine vein graft model, showed that placement of an external stent on the vein reduces the occlusion rate[17], and that the beneficial action of the stent is due, at least in part, to preservation of the nitric oxide system[18].

The adventitia and cushion of surrounding tissue that remains intact after harvesting by the no-touch technique

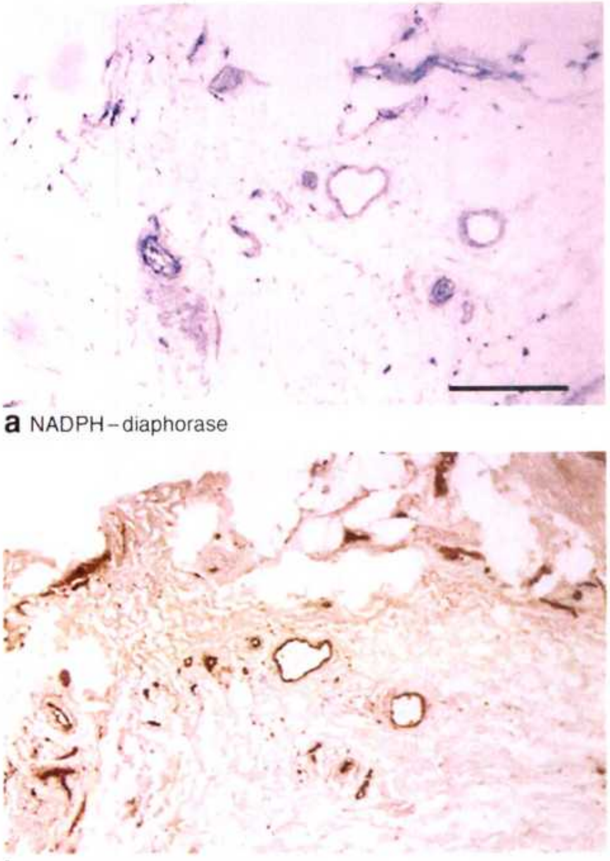


Fig. 5 Reduced nicotinamide adenine dinucleotide phosphate (NADPH)–diaphorase histochemistry and CD31 immunohistochemistry. **a** Nitric oxide synthase identification within the adventitia of a vein segment harvested by the no-touch method. There are regions of blue staining (NADPH–diaphorase), many associated with microvessels and vasa vasorum, which are identified in **b** by means of CD31 immunohistochemistry. Scale bar, 100 μm

has a high collagen content and may therefore act as a buffer against pulsatile stress. There is also evidence that adventitial injury is involved in vessel occlusion, via activation of adventitial fibroblasts[19] and local tissue ischaemia as a result of damage to adventitial microvessels[20]. Preservation of the adventitia has been suggested to improve vein graft patency[21]. In canine jugular vein the endothelium is sensitive to a maintained blood supply via the vasa vasorum. The risk of ischaemic injury to a vein graft is partially overcome when the vein is dissected *en bloc* with its surrounding fat and accompanying vasa vasorum during operation.

Another important contributing factor, however, is injury to the saphenous vein during surgical preparation. Although previous no-touch techniques have been described in an attempt to reduce the incidence of vein graft occlusion[7,8], these vessels are usually still distended after harvesting. In the present study endothelial integrity (assessed by means of the endothelium-specific antibody CD31) was better maintained using the described no-touch technique for vein graft harvesting. Electron microscopic findings in a previous study of this no-touch technique of vein harvesting show preserved endothelium[7]. Scanning electron microscopy revealed a more pronounced endothelial denudation effect following conventional vein preparation.

NADPH–diaphorase staining and NOARG binding, as indicators of putative activity, suggest that NOS availability is also preserved on the luminal endothelium of grafts harvested by the no-touch method. Vessels harvested by this technique might maintain their nitric oxide-producing capacity *in vivo*, which could reduce the incidence of vessel occlusion by promoting vasodilatation and reducing platelet aggregation and thrombus formation.

Apart from being located on the luminal endothelium, NOS was also associated with microvascular endothelium within the adventitia. As the adventitia plays an important role in intimal hyperplasia and atherosclerosis[21,22], the adventitial vasa vasorum may be involved by acting as an important source of nitric oxide to the media.

The no-touch technique of vein graft harvesting described here has resulted in a low early occlusion rate in a prospective study of coronary artery bypass surgery. The preservation of endothelial and adventitial sources of nitric oxide by the no-touch technique of vein harvesting could play a major role in improving vein graft patency rates.

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Original article

Quality of life after low anterior resection with total mesorectal excision and temporary loop ileostomy for rectal carcinoma

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Background: Low anterior resection (LAR) with total mesorectal excision (TME) may be the optimal operation for carcinoma of the mid or lower rectum. Routine formation of a temporary defunctioning stoma has been recommended with TME. The impact of this strategy on health-related quality of life (HRQOL) has not been addressed.

Methods: A prospective longitudinal study was conducted among 24 patients undergoing LAR with TME and loop ileostomy for rectal cancer. Clinical outcomes were documented. HRQOL was assessed using Short Form 36 (SF-36). Twenty-three patients undergoing high anterior resection (HAR) for rectosigmoid cancer were studied concurrently to determine the effects of major colorectal resection without a stoma.

Results: Time to resume normal diet, length of stay in hospital and time to return to non-work activities were similar after HAR or LAR with TME and loop ileostomy. Twelve weeks after HAR SF-36 scores were stable or improved compared with preoperative levels. In contrast, 12 weeks after LAR + TME patients had a reduction in physical functioning scores on SF-36. SF-36 scores improved after ileostomy closure. Ileostomy closure increased total hospital stay and time off non-work activities.

Conclusion: LAR with TME and temporary loop ileostomy for rectal cancer results in a long total hospital stay and impairs aspects of HRQOL. Prompt stoma closure should be a priority in these patients.

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Introduction

Low anterior resection (LAR) with total mesorectal excision (TME) is increasingly regarded as optimal surgical treatment for potentially curable carcinoma of the mid and lower rectum[1,2]. Local recurrence rates below 5 per cent have been achieved in large series after potentially curative resection[3–5]. The operation necessitates an anastomosis close to the pelvic floor. Such low anastomoses have been associated with rates of clinical anastomotic leakage ranging from 3 to 17 per cent[6–11]. Several authors recommend routine formation of a defunctioning stoma when performing LAR with TME to reduce the impact of anastomotic leakage[6,12,13]. Others use a defunctioning stoma selectively[7,8,14]. A temporary stoma and the need for a second operation for closure are potentially significant additional burdens for the patient. The aim of this study was to determine the impact of a strategy of LAR with TME and routine temporary loop ileostomy on health-related quality of life (HRQOL) in the months following operation.

Patients and methods

Patients with cancer of the mid or low rectum who had been assigned to treatment by LAR with TME and loop ileostomy were studied prospectively. A contemporaneous group of patients undergoing high anterior resection (HAR) for carcinoma of the upper rectum or distal sigmoid colon was studied to evaluate the effect of major colorectal resection without a stoma.

Recruitment took place after the patient had been counselled by the surgical team and stoma therapist about the nature of the disease process, the operation planned and the potential need for a temporary stoma. Demographic details, operative findings and course in hospital were documented. Global HRQOL was assessed using Short Form 36 (SF-36). SF-36 is a well validated general health questionnaire which examines eight dimensions of health from the patient's viewpoint[15]. These dimensions are physical function, role limitations due to physical functioning, general mental health, role limitations due to emotional problems, bodily pain, vitality, social functioning and general health perception.

To allow within-group comparisons over time, SF-36 questionnaires were administered before operation, 12 weeks after operation (LAR and HAR) and 6 weeks after ileostomy closure (LAR only). Recruitment and administration of questionnaires were carried out by a dedicated research nurse (C.J.F.) who was not otherwise involved in the care or counselling of patients. At each time point patients were asked to provide data on time to return to work (where relevant) and to non-work activities, and to volunteer up to three ongoing concerns regarding their illness or management.

LAR with TME was carried out as described previously, with anastomosis close to the pelvic floor and routine formation of a loop ileostomy[16]. In HAR the mesorectum and rectum were divided 5 cm distal to the tumour and the anastomosis was to the mid rectum.

The research protocol was approved by the West Gloucestershire Local Research Ethics Committee.

Statistical analysis

Data are presented as mean(s.d.) unless otherwise indicated. For each of the eight dimensions on SF-36, item scores were coded, summed and transformed on to a scale of 0 (worst) to 100 (best)[17,18]. Within each group comparisons were made between postoperative and preoperative SF-36 scores using Wilcoxon matched-pairs signed rank test. No attempt was made to compare the groups statistically as this would have been inappropriate.

Results

Fifty-two patients were enrolled in the study of whom five were withdrawn because of extensive disease found at laparotomy. The groups were comparable before operation with regard to demographic details and independence (*Table 1*). The proportion of potentially curative resections and distribution of Dukes' stages was similar between the groups.

Table 1 Patient characteristics

	LAR + TME	HAR
No. of patients	24	23
Sex ratio (M : F)	16 : 8	17 : 6
Mean (range) age (years)	67 (50–84)	71 (46–89)
Independent	21	20
Retired	16	17
Co-morbidity	3	8

LAR + TME, low anterior resection with total mesorectal excision; HAR, high anterior resection

Table 2 Management and outcome

	LAR + TME	HAR
No. of patients	24	23
Curative	23	21
Dukes' stage		
A	5	5
B	10	8
C	8	9
Time to full diet (days)*	6(4)	7(2)
Discharged home	24	22
Hospital stay for resection (days)*	12(6)	12(5)
Time off non-work activities (weeks)*	7(6)	6(2)
Total hospital stay (days)*	19(7)	12(5)
Total time off non-work activities (weeks)*	11(6)	6(2)

*Values are mean(s.d.). Total hospital stay and time off non-work activities in the low anterior resection with total mesorectal excision (LAR + TME) group includes ileostomy closure. HAR, high anterior resection

Clinical outcomes

There were no deaths following resection in either group. Complications after LAR + TME included pelvic abscess (one), high ileostomy output (one) and peristomal abscess (one).

Times to resume eating after resection, length of stay in hospital and time to return to non-work activities were similar after LAR + TME and HAR (*Table 2*). Few of the patients had been in employment before operation. The majority of patients (46 of 47) returned home, usually with additional support arrangements. Only one patient required placement in residential care (after HAR).

After LAR + TME, patients required visits from stoma therapists on a mean of 4 (range 0–32) occasions and nine required visits by the family doctor (compared with none after HAR). For 15 patients ileostomy leakage was a problem. Ten patients had crises at home related to their stoma, mostly due to leakage. Ileostomies were closed after

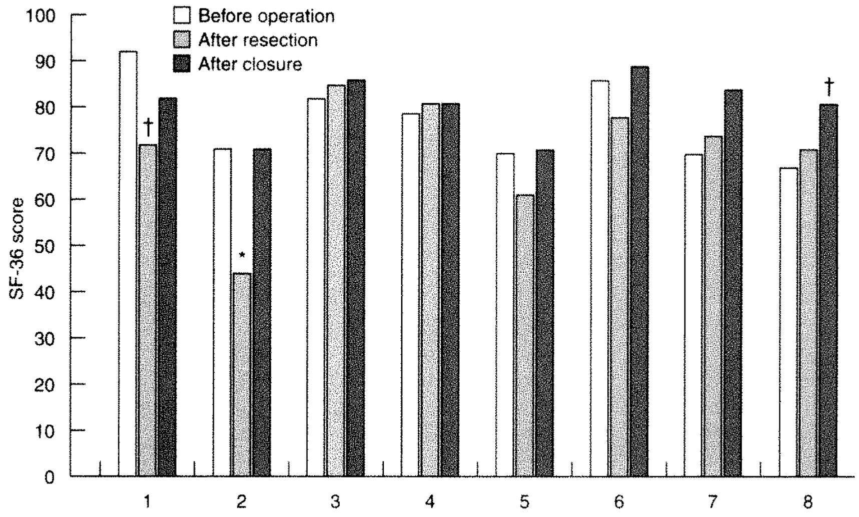

Fig. 1 Impact of low anterior resection with total mesorectal excision and loop ileostomy on mean Short Form 36 (SF-36) scores. 1, physical functioning; 2, physical role limitation; 3, bodily pain; 4, general health perception; 5, vitality; 6, social functioning; 7, emotional role limitation; and 8, mental health. $^*P < 0{\cdot}05$, $^\dagger P < 0{\cdot}01$ *versus* before operation (Wilcoxon matched-pairs signed rank test)

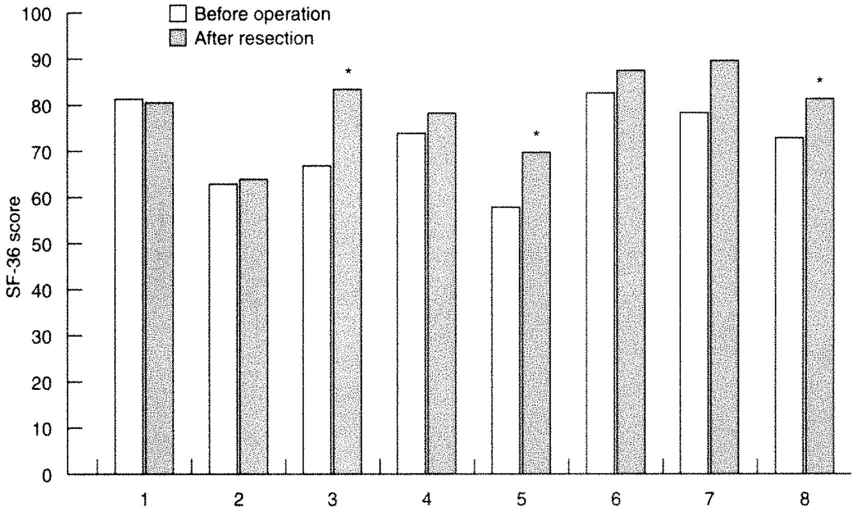

Fig. 2 Impact of high anterior resection on mean Short Form 36 (SF-36) scores. 1, physical functioning; 2, physical role limitation; 3, bodily pain; 4, general health perception; 5, vitality; 6, social functioning; 7, emotional role limitation; and 8, mental health. $^*P < 0{\cdot}05$ *versus* before operation (Wilcoxon matched-pairs signed rank test)

a mean of 23(9) weeks after operation (rather than at 12 weeks as planned). Causes for delay included chemotherapy (Dukes' C only), anastomotic defects on contrast enema and hospital waiting lists. Stoma closure resulted in a total mean hospital stay of 19(7) days in this group. Mean total time off non-work activities was 11(6) weeks following LAR compared with 6(2) weeks after HAR.

Patients' concerns

Before LAR + TME patients' most frequent concerns were the operation itself (11) and cancer (10). Only three patients volunteered stoma-related concerns. Twelve weeks after resection patients' most frequent concerns were stoma closure (9), cancer recurrence (8) and continued health (4). Six weeks after ileostomy closure their principal concern was bowel function (11). Before HAR patients' most frequent concerns were the operation itself (9) and cancer (7). Twelve weeks after resection their most frequent concerns were their continued health (12) and cancer recurrence (8).

Short Form 36 scores

Twelve weeks after LAR + TME patients had a significant reduction in mean physical functioning scores on SF-36 (72(26) *versus* 92(9) before operation; $P < 0{\cdot}01$) and a significant decrease in physical role scores (44(41) *versus* 71(43) before operation; $P < 0{\cdot}05$) (*Fig. 1*). SF-36 scores improved by 6 weeks after ileostomy closure. The score for mental health was significantly better after ileostomy closure than before resection (81(17) *versus* 67(19); $P < 0{\cdot}01$).

Twelve weeks after HAR patients had significant improvements in mean scores on SF-36 for bodily pain (84(24) *versus* 66(27); $P < 0{\cdot}02$), vitality (70(17) *versus* 58(23); $P < 0{\cdot}04$) and mental health (82(15) *versus* 73(15); $P < 0{\cdot}05$) compared with preoperative values (*Fig. 2*).

Discussion

A strategy of LAR with TME and routine temporary loop ileostomy produced a measurable impairment in global HRQOL in the months after resection, which improved after ileostomy closure.

The prospective longitudinal study design enabled patients to act as their own controls in assessing the impact of operation on quality of life. Comparison with a group of patients having LAR without temporary loop ileostomy would have been inappropriate on account of the increased likelihood of morbidity from anastomotic leakage[6,10,11], and was not warranted by the aims of the study.

HRQOL was evaluated by means of a well validated global health questionnaire (SF-36)[15,19]. SF-36 discriminates between symptomatic and asymptomatic patient groups, different stages and differing severities of disease[19], has been found to reflect changes in global health perception with time in a range of cancers[18,20] and is used in rectal cancer trials[21]. The recently validated European Organization for Research and Treatment of Cancer QLQ-CR38 colorectal cancer questionnaire may well prove advantageous for future studies of this nature[22].

LAR with TME, as performed for low rectal cancer, is an operation of greater magnitude than the HAR indicated for tumours of the upper rectum or rectosigmoid[1]. Nonetheless, patients appeared to recover from each type of resection at similar rates, as judged by their time to resume normal diet, length of stay in hospital and time to return to non-work activities. No patient became dependent as a consequence of having a stoma. Such objective measures of clinical outcome did not, however, reflect effects on patients' perceptions of global quality of life. Whereas patients' scores on SF-36 were generally improving 12 weeks after HAR, scores for physical functioning and physical role were worse 12 weeks after LAR with TME and loop ileostomy (despite objective evidence of recovery). The authors speculate that the temporary ileostomy contributed to this difference in perceived quality of life after LAR. SF-36 scores improved towards preoperative levels after ileostomy closure. The need for ileostomy closure increased total hospital stay and time out of non-work activities considerably.

Most studies suggest that a number of dimensions of quality of life are worse in patients with a permanent stoma than in those without one after rectal resection for cancer[23–26]. Patients with a temporary stoma also suffer an impaired HRQOL[27]. The present study provides new insights into the reasons for this deterioration in the setting of rectal cancer.

Before operation patients appeared to be most concerned about the implications of a diagnosis of cancer and the need for a major operation. A temporary stoma is an unexpected additional burden, the implications of which are not fully appreciated before operation. This may reflect the patient's preoccupation with cancer and operation, the short time frame within which diagnosis and management take place, and the idea that the stoma is in any case only going to be temporary. After operation, the stoma becomes a major focus of the patient's attention. Patients required considerable input from their family doctor and the stoma therapy service; several had crises related to stoma leakage. Compared with the preoperative state, patients' perception of HRQOL was impaired until the stoma was closed, often several months later.

Temporary loop ileostomy appears to reduce leak-related morbidity and mortality rates after LAR with TME[6,10,11]. Leaks may occur but they require reoperation less often and result in a permanent stoma less frequently. However, the cost to patients of routine loop ileostomy appears to be an impaired quality of life, prolonged interference with daily activities, a second inpatient stay and operation to close the stoma, together with a small but definite risk of complications related to the ileostomy or its closure. Large numbers of patients are significantly inconvenienced, to avoid reoperation for leakage in perhaps 8–16 per cent[6,7,11]. Given these considerations, some groups use defunctioning stomas 'selectively' or rarely, accepting the need for reoperation in a proportion of their patients[7,8,14]. Clearly, more reliable anastomotic techniques, better means of selecting for stomas those patients at highest risk of anastomotic leakage, or better methods of protecting at-risk anastomoses are required. Meanwhile, units that adopt a policy of routine temporary loop ileostomy when performing LAR need to provide increased resources for stoma therapy and inpatient surgical care. They should also recognize the effect of this strategy on HRQOL and close these temporary stomas promptly.

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Original article

Population-based study of factors influencing occurrence and prognosis of local recurrence after surgery for rectal cancer

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Background: Few data are available from population-based statistics on the risk of local recurrence after surgery for rectal cancer. The aims of this study were to determine factors influencing local control and to analyse treatment and prognosis of recurrences in a well defined population.

Methods: Data were obtained from the cancer registry of the Côte d'Or (France). From 1976 to 1995, 682 patients resected for cure for a rectal carcinoma were included. Recurrence rates and survival rates were calculated using actuarial methods. A relative survival analysis and Cox multivariate analysis were performed.

Results: During the study 135 local recurrences were registered. The 5-year cumulative local recurrence rate was 22·7 per cent. In multivariate analysis the two variables significantly associated with local recurrence risk were stage at diagnosis and the macroscopic type of growth. There was a non-significant decrease in local recurrence rate in patients treated by preoperative radiotherapy compared with that in patients treated by surgery alone. The proportion of patients re-resected for cure was 25·2 per cent, and increased from 13·0 per cent in 1976–1985 to 37·9 per cent in 1986–1995 ($P = 0.001$). The 5-year relative survival rate was 13·6 per cent overall and 40·6 per cent after resection for cure ($P < 0.001$).

Conclusion: Local recurrence of rectal cancer following resection remains a substantial problem. Improvement can be expected from better care and earlier diagnosis.

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Introduction

Cancer of the rectum is a serious health problem. The number of new cases in 1995 in France was estimated to be 11 500[1] and the crude 5-year survival rate was 38 per cent[2]. The primary treatment remains surgical resection with or without adjuvant radiotherapy. Local recurrence after curative surgery is a major reason for failure. A wide range of local recurrence rates has been reported in the literature. Recurrence probably depends on the characteristics of the cancer at the time of diagnosis and on the quality of the surgical procedure. Various clinical and pathological indicators of local failure have been described[3]. Most available data relating to follow-up after curative surgery are hospital based and cannot be regarded as reference values because of potential selection bias. However, knowledge of failure patterns is necessary for prediction of outcome and stratification of patients entering follow-up programmes or adjuvant trials. Community-based studies are the best way of clarifying the natural history of a disease following resection for cure. They are difficult to perform because they require active participation of the entire medical profession. The aims of this study were to determine the factors influencing local control after potentially curative treatment for rectal cancer, using data from a population-based series in France, and to analyse the results of treatment of recurrence.

Patients and methods

Population

A population-based cancer registry including all digestive tract cancers covers the resident population of the well defined administrative area of Côte d'Or (Burgundy, France; 494 000 inhabitants according to the 1990 census). Cancer registration began in 1976. Accurate data relative to clinical features, characteristics of tumours, treatment and follow-up are included. They are obtained regularly from pathologists, hospital and private physicians (gastroenterologists, surgeons, oncologists, radiotherapists and general practitioners) as well as from public administration (death certificates).

Rectal cancers were defined as tumours arising from the rectal ampulla only, i.e. cancers located within 15 cm of the anal verge. Altogether 1120 cases fitted this definition. Cancers of the rectosigmoid junction (*n* = 502) and anal canal (*n* = 36) were not included in the study. Excluded patients were those not resected for cure (*n* = 418), patients who died within 30 days of surgery (*n* = 46), and those with non-epithelial tumours (*n* = 48) or cancers with a synchronous metastasis resected for cure (*n* = 10). The remaining 682 patients, with a carcinoma of the rectal ampulla resected for cure between 1976 and 1995 in Côte d'Or, were used to calculate the local recurrence rate. Surgery was considered curative when the surgeon deemed the tumour to be completely removed and the distal margins free from cancer.

Data about recurrence were not collected routinely. Two special studies were conducted in order to collect these data. The first was performed in 1987 and dealt with patients diagnosed between 1976 and 1984, and the second in 2000 with patients diagnosed between 1983 and 1995. Information about recurrence was obtained from all clinicians (specialists as well as general practitioners) involved in the management and follow-up of patients. Local recurrence was defined as any histological, morphological or clinical evidence of recurrence of rectal carcinoma in the pelvis, either alone or in association with distant metastasis. The date of diagnosis of the local failure, as well as the eventual treatment and the date of death, were also recorded.

Studied variables

For all patients, the studied variables included sex, age at diagnosis, pathological reports and treatment. Tumour location within the rectum was classified into two groups: less than 8 cm from the anal verge (*n* = 363) and 8 cm or more from the anal verge (*n* = 292). Tumour location was not recorded in 27 patients.

Surgical procedures were divided into abdominal resections (anterior resection including Hartmann's procedure and coloanal anastomosis), abdominoperineal resections and transanal excisions (including transanal surgery and endoscopic polypectomy). The operations were carried out in nine institutions (two university units, three local hospitals and four private hospitals) by 29 surgeons. Adjuvant radiotherapy treatment was divided into preoperative (*n* = 95) and postoperative (*n* = 129) treatment. Postoperative radiotherapy only was used until 1990, after which it has been replaced progressively by preoperative radiotherapy. Adjuvant chemotherapy was given in only 25 patients.

Cancer extension was coded according to the 1997 version of the tumour node metastasis (TNM) classification of malignant tumours[4] in three stages: stage 1, limited to the rectal wall (T_{1-2}, N_0, M_0); stage 2, extension beyond the rectal wall (T_{3-4}, N_0, M_0); and stage 3, lymph node involvement (all T, N_{1-2}, M_0). The tumour size and macroscopic growth pattern were also obtained from pathology reports. Growth configuration was classified into three groups: fungating tumours (*n* = 210), ulcerofungating tumours (*n* = 162) and ulceroinfiltrating tumours (*n* = 291). The eight infiltrative cancers were recorded within the last category. For 19 patients no information about growth pattern was available. Distal margins for anterior resection procedures were measured before tissue fixation on an unpinned specimen. Treatment of local recurrence was divided into repeat resection for cure, palliative resection, chemotherapy or radiotherapy, or both, and symptomatic treatment. In May 2000, the local recurrence status of 665 patients (97·5 per cent) was available.

Statistical analysis

Crude local recurrence rates were calculated using actuarial survival methods and were expressed with standard errors. The curves were compared using the log rank test. Patients who died from intercurrent disease were censured at time of death, and patients who developed a local recurrence were censured at time of recurrence. Recurrence rates were not calculated when the number of cases was less than 20 in a subgroup. Overall recurrence rates were calculated as well as recurrence rates according to therapeutic modalities: surgery alone (*n* = 458), preoperative radiotherapy (*n* = 95) and postoperative radiotherapy (*n* = 129). A multivariate survival analysis was performed using Cox's proportion hazards regression model.

Crude survival rates after local recurrence were calculated using the actuarial method. Relative survival rates were also calculated, these being defined as the ratio of the observed survival rate to the expected survival rate derived from the Côte d'Or area mortality table. Relative survival rates after recurrence were calculated using Relsurv 2·0™ software package[5].

Results

Univariate analysis

Among the 682 patients involved in the study there were 135 local recurrences (19·8 per cent), which occurred within 3 years after the diagnosis in 94·4 per cent of patients. Fifty-three patients (39·3 per cent) also developed distant metastasis: six before local recurrence, 31 after local recurrence and 16 with synchronous distant metastasis.

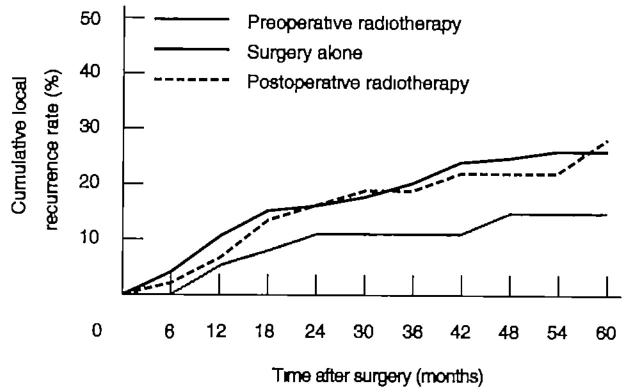
Table 1 shows the 1-, 2-, 3- and 5-year actuarial cumulative risk of recurrence according to period of diagnosis, sex, age, location of tumour, type of surgical procedure, adjuvant radiotherapy, TNM classification, tumour size, macroscopic growth and size of distal margin. The overall local failure rate was 9·1 per cent at 1 year and 22·7 per cent at 5 years. Sex, age, period of diagnosis and tumour location did not significantly influence the local recurrence rate. A significant increase in the cumulative local recurrence rate was noted with advancing stage at diagnosis: the 5-year cumulative recurrence rate varied from 10·2 per cent for stage 1 cancer to 40·5 per cent for stage 3 ($P < 0·001$). Not surprisingly the type of tumour resection influenced the recurrence rate. It was lower after transanal resection than after abdominal or abdominoperineal resection. The recurrence rate was similar after abdominal resection and abdominoperineal resection.

The local recurrence rate was influenced by the macroscopic type of growth. Ulceroinfiltrating and ulcerofungat-

Table 1 Cumulative local recurrence rates after resection for cure of rectal cancer

	No. of patients	No. of local recurrences	Cumulative local recurrence rate (%)				*P*
			1 year	2 years	3 years	5 years	
All patients	682	135	9·1(1·2)	15·3(1·5)	18·7(1·6)	22·7(1·8)	
Period of diagnosis							n.s.
1976–1985	327	67	8·6(1·7)	15·7(2·2)	21·1(2·6)	25·7(2·8)	
1986–1995	355	68	9·5(1·6)	14·9(2·0)	16·7(2·1)	20·3(2·4)	
Sex							n.s.
Male	424	89	9·1(1·5)	16·9(2·0)	20·4(2·2)	26·0(2·5)	
Female	258	46	9·0(1·9)	12·7(1·9)	16·1(2·5)	17·8(2·6)	
Age (years)							n.s.
≤ 70	328	57	9·6(1·8)	15·3(2·2)	18·7(2·5)	21·5(2·7)	
> 70	354	78	8·6(1·6)	15·2(2·0)	18·7(2·2)	23·6(2·5)	
Tumour location (cm)							n.s.
≥ 8	292	61	8·8(1·8)	15·4(2·3)	19·4(2·5)	24·1(2·8)	
< 8	363	73	9·3(1·6)	15·7(2·1)	18·8(2·3)	22·6(2·5)	
Surgical procedure							0·033
Transanal	84	10	5·2(2·5)	5·2(2·5)	10·7(3·6)	12·2(3·8)	
Abdominal resection	226	52	11·7(2·2)	19·1(2·8)	22·5(3·0)	26·6(3·3)	
Abdominoperineal resection	372	73	8·4(1·5)	15·4(2·1)	18·2(2·3)	23·0(2·6)	
Adjuvant radiotherapy							n.s.
None	458	88	9·0(1·4)	14·7(1·8)	18·1(2·0)	22·4(2·3)	
Preoperative	95	14	10·4(3·3)	14·1(3·8)	14·1(3·8)	15·7(4·0)	
Postoperative	129	33	8·2(2·5)	17·9(3·5)	23·8(4·0)	29·0(4·5)	
TNM stage							< 0·001
1	211	23	1·6(0·9)	5·1(1·7)	7·5(2·0)	10·2(2·4)	
2	249	54	8·9(1·9)	15·0(2·4)	18·1(2·6)	24·1(3·1)	
3	193	58	19·2(3·1)	30·3(3·8)	36·9(4·2)	40·5(4·4)	
Tumour size (cm)							0·001
≤ 3	195	21	5·0(1·6)	6·8(1·9)	8·6(2·1)	10·8(2·4)	
> 3 – ≤ 6	385	91	10·3(1·6)	18·4(2·2)	22·5(2·4)	28·2(2·7)	
> 6	102	23	13·0(3·7)	21·3(4·6)	26·0(5·1)	27·9(5·3)	
Macroscopic growth							< 0·001
Fungating	210	27	2·7(1·2)	6·7(1·9)	12·1(2·5)	14·1(2·7)	
Ulcerofungating	162	41	14·6(2·9)	20·6(3·4)	22·2(3·5)	29·8(4·1)	
Ulceroinfiltrating	291	67	11·1(2·0)	19·6(2·5)	22·6(2·7)	26·3(3·0)	
Distal margin (mm)*							0·006
≤ 20	143	26	8·3(2·4)	14·0(3·1)	15·7(3·2)	20·8(3·8)	
> 20	83	26	17·7(4·5)	28·5(5·4)	35·7(6·0)	37·6(6·1)	

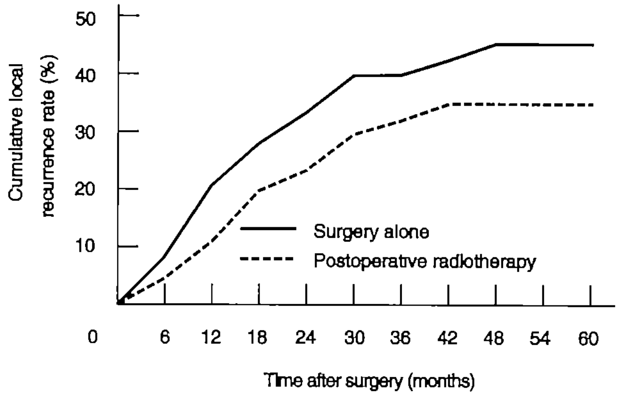
Values in parentheses are s.e.m. *Patients treated by anterior resection. TNM, tumour node metastasis; n.s., not significant



No at risk

Preoperative radiotherapy	42	38	36	34	32	30	29	26	23	22	18
Surgery alone	160	134	122	109	106	99	95	83	78	71	63
Postoperative radiotherapy	47	44	41	37	33	31	29	28	26	23	20

Fig. 1 Cumulative local recurrence rate by treatment procedure for tumour node metastasis stage 2 rectal cancer



No. at risk

Surgery alone	110	78	60	45	33	27	24	22	18	15	14
Postoperative radiotherapy	66	60	53	46	41	32	27	23	22	17	16

Fig. 2 Cumulative local recurrence rate by treatment procedure for tumour node metastasis stage 3 rectal cancer

ing types showed a higher incidence of recurrence than fungating lesions. Local recurrence was also influenced by tumour size: recurrence was more frequent after resection of tumours above 3 cm in size than after excision of smaller tumours. Following anterior resection the local recurrence rate was higher when the length of the distal margin exceeded 20 mm than with a shorter distal margin.

Patients were divided into three groups according to treatment (*Table 1*). The overall local recurrence rate was lower in patients treated with preoperative radiotherapy than in those treated with postoperative radiotherapy or surgery alone, but the difference between the recurrence curves was not significant. As the indication for adjuvant treatment is influenced by stage, local recurrence rates were considered according to the TNM tumour stage. For TNM stages 1 and 2 the local recurrence rate was lower in patients who received preoperative radiotherapy than in those treated with surgery alone or postoperative radiotherapy; however, the difference was not significant (*Fig. 1*). The number of patients was too small to calculate cumulative local recurrence rates in patients with TNM stage 3 tumours treated with preoperative radiotherapy. In stage 3 there was a tendency towards a lower recurrence rate in patients who received postoperative radiotherapy than in those treated with surgery alone (*P* not significant) (*Fig. 2*). In these two groups of patients, the cumulative local recurrence curves were similar to those calculated for stage 2. The number of patients with stage 1 tumours treated with postoperative radiotherapy was too small to calculate a cumulative local recurrence rate.

Multivariate analysis adjusted for sex and age

The relative risk of local recurrence obtained with the Cox model is given in *Table 2*. There were two variables significantly associated with the risk of local recurrence. Stage at diagnosis was the strongest pronostic factor; there was a fourfold increase in the relative risk of recurrence of stage 3 lesions compared with stage 1 tumours. Macroscopic growth remained significant in the multivariate analysis: the relative risk of local failure was nearly twice as high for ulcerofungating and ulceroinfiltrating tumours than for fungating tumours. Tumour size and type of surgical treatment were not significantly associated with recurrence.

Table 2 Multivariate analysis of factors associated with local recurrence

	Relative risk	*P*
TNM stage		
1	1	
2	2·0 (1·16–3·36)	< 0·001
3	3·9 (2·23–6·75)	< 0·001
Macroscopic growth		
Fungating	1	
Ulcerofungating and ulceroinfiltrating	1·6 (1·03–2·56)	0·018

Values in parentheses are 95 per cent confidence intervals. TNM, tumour node metastasis

Treatment of local recurrence

Among patients with a local recurrence, resection for cure was performed in 34 cases (25·2 per cent), palliative surgery in 18 (13·3 per cent), radiotherapy alone in 40 (29·6 per cent), in association with chemotherapy in one (0·7 per cent), chemotherapy alone in five (3·7 per cent) and treatment of symptoms in 34 (25·2 per cent). The treatment offered was unknown in three patients (2·2 per cent). The proportion of patients resected for cure increased from 13·0 per cent in 1976–1985 to 37·9 per cent in 1986–1995 ($P = 0{\cdot}001$).

Survival rates decreased dramatically with time. The 1- and 5-year crude survival rates were 45·4 and 11·0 per cent respectively. The corresponding relative survival rates were 47·4 and 13·6 per cent. There was a trend towards increased survival between the two 10-year periods: the 5-year relative survival rate rose from 9·0 to 18·8 per cent (*P* not significant). Patients aged less than 70 years had a better relative survival rate than older patients (17·8 and 7·2 per cent respectively at 5 years; $P = 0{\cdot}04$). The treatment offered was an important determinant of prognosis. The 5-year relative survival rate ranged from 40·6 per cent in patients resected for cure to 1·7 per cent in those treated symptomatically ($P < 0{\cdot}001$) (*Table 3*).

Discussion

This study has the advantage of including all patients with rectal cancer resected for cure in a well defined French population over a 20-year interval. The multiplicity of information sources permits the assumption that nearly all newly diagnosed cases were recorded. Information on treatment, stage at diagnosis and other morphological

Table 3 Relative survival rates after local recurrence for rectal cancer (relative survival model using the Côte d'Or area mortality table)

	No. of patients	Relative survival rate (%)			*P*
		1 year	3 years	5 years	
All patients	135	47·4(4·4)	17·4(3·4)	13·6(3·3)	
Age at diagnosis (years)					0·04
≤ 70	57	53·1(5·1)	22·2(4·7)	17·8(4·5)	
> 70	78	37·9(6·0)	9·9(3·7)	7·2(3·2)	
Treatment*					< 0·001
Resection for cure	34	74·9(5·7)	46·3(8·7)	40·6(9·2)	
Palliative resection	18	46·1(9·6)	12·3(6·9)	8·8(5·9)	
Radiotherapy or chemotherapy	46	42·9(6·4)	10·1(4·1)	7·0(3·6)	
Symptomatic treatment	34	27·1(6·9)	2·9(2·1)	1·7(1·4)	
Period of diagnosis					n.s.
1976–1985	67	41·9(5·3)	12·1(3·8)	9·0(3·4)	
1986–1995	68	54·6(5·9)	23·0(5·3)	18·8(5·2)	

Values in parentheses are s.e.m. *Unknown for three patients. n.s., Not significant features was available for nearly all patients and follow-up data were found for 96 per cent of recorded cases. The study was therefore carried out without the referral bias that often occurs in hospital-based series.

In this community-based study the 5-year cumulative rate of local recurrence after resection for cure of rectal cancer was high (22·7 per cent). This finding is similar to, or lower than, values reported in most other studies, which have reported local recurrence rates of between 25 and 37 per cent[6–11]. It is also comparable to the proportion of local recurrences reported in the reference arm of trials that have compared surgery alone to combined surgery and radiotherapy. A review of these studies by Påhlman[12] indicated that the local recurrence rate ranged between 23 and 41 per cent with a mean of 27 per cent. However, some authors have reported lower recurrence rates, mainly in patients treated by total mesorectal excision[13–17]. Although there are no available data concerning total mesorectal excision in this study, it is probable that very few patients were treated in this way as recruitment ended in 1995. Although no randomized study is available, there is evidence that local recurrence rates are lower with this technique than with conventional surgery[18]. Available results suggest that the local recurrence rate may be less than 10 per cent. A recent study has underlined the benefit of a training progamme on total mesorectal excision on the outcome of rectal cancer[19].

An important element of progress identified in the study was the increase in continence-preserving operations from 19·6 per cent (1976–1985) to 45·8 per cent (1986–1995)[20]. This is due in part to shortening of distal margins (a distal clearance of 1 cm below the tumour in an unfixed and unpinned specimen may be adequate in most instances[21,22]) and use of circular endoluminal staplers, which have been employed widely in France since 1985. In the present study the number of patients with a distal margin of less than 20 mm changed over time from 50·0 per cent (1976–1985) to 68·5 per cent (1986–1995). Data in this study confirm that the increasing percentage of short distal margins was not associated with an increase in local recurrences. In fact local recurrence was more frequent when the distal margin exceeded 20 mm and corresponded more frequently to larger tumours at diagnosis. The skill and experience of the surgeon performing the operation may also influence local recurrence rates[3,23].

Another factor that may influence outcome is adjuvant radiotherapy. Trials have indicated that radiotherapy may reduce local recurrence rates. It is now known that preoperative radiotherapy does this more effectively[24] and that it also increases overall survival[25]. The present study represented an opportunity to evaluate the effect of radiotherapy on local recurrence in common practice. Comparison of the overall local recurrence rate according to adjuvant treatment is difficult because indications are not strictly comparable. Postoperative radiotherapy is indicated for TNM stage 2 and 3 disease, while preoperative radiotherapy may be given for all stages. This is why the results were considered according to the stage at diagnosis. The practice of adjuvant therapy increased over time from 18·9 per cent (1976–1980) to 48·6 per cent (1991–1995). Data reported here suggest that preoperative radiotherapy decreases local recurrence in stages 1 and 2 compared with surgery alone. Radiotherapy results confirm the limited effect of postoperative radiotherapy, which was seen only in patients with stage 3 disease.

Another purpose of this study was to identify clinical or pathological characteristics available in a population-based series that influence the risk of local recurrence. Stage at diagnosis played an important role. It is the most important determinant of the risk of local recurrence. The morphological appearance of the tumour was also associated with local recurrence risk after adjusting for other potential prognostic factors. Other authors have already reported that exophytic tumours are associated with a lower recurrence rate than other lesions[26,27]. Ulcerating tumours may diffuse more rapidly to perivisceral fat and nodes. Tumour size and the type of surgical procedure were not significant prognostic factors, according to multivariate analysis, because they are very closely correlated with stage at diagnosis. The available data in this study did not allow study of the prognostic significance of tumour differentiation, blood and lymphatic invasion, or extent of lateral margins. No differences were found in recurrence rate after abdominal resection compared with abdominoperineal resection.

The survival rate after recurrence is low. Half the patients died within 1 year and only about 10 per cent survived 5 years after the local recurrence. This study confirmed that a radical resection must be performed whenever possible. It was performed in one-quarter of the present patients and was the only way to achieve long-term survival[28,29]. Palliative resection and/or radiotherapy can improve patient comfort, but the survival rate is poor (less than 10 per cent after 5 years).

Substantial advances in the management of local recurrence of rectal cancer were evident when the first 10-year period was compared with the second interval. There was a threefold increase in the radical resection rate and a twofold increase in the 5-year survival rate. However, further improvements must be made in order to increase survival. These may be achieved through earlier diagnosis, use of total mesorectal excision, and development of effective adjuvant or palliative treatments.

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Original article

Patient accuracy of reporting on hereditary non-polyposis colorectal cancer-related malignancy in family members

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Background: The cancer family history is important in identifying individuals with hereditary non-polyposis colorectal cancer (HNPCC). The accuracy of a suspected HNPCC family history reported by patients with colorectal cancer was evaluated.

Methods: This was a prospective population-based study including consecutive patients with colorectal cancer. A questionnaire covering the occurrence of malignancy among relatives was completed.

Results: A total of 1200 patients with colorectal cancer completed the questionnaire. Fulfilment of Amsterdam criteria I or II according to the patients' reports was rejected in three of 14 cases (false-positive rate 21 per cent). Furthermore, seven of 18 probands whose families met the Amsterdam criteria I or II after verification were identified by further exploration in families who, according to the probands, met weaker criteria (false-negative rate 39 per cent).

Conclusion: The present study suggests that family studies on HNPCC are not reliable unless the diagnoses of family members are verified from official sources. If endoscopic screening is offered entirely on the basis of unverified information from patients with colorectal cancer, there is a risk that a large proportion of the families will not be offered relevant surveillance.

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Introduction

Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant cancer syndrome characterized by early-onset colorectal cancer and other gastrointestinal and urogenital cancers[1–4]. The mean age at the time of colorectal cancer development is approximately 45 years[5–7]. HNPCC is diagnosed by detecting pathogenic mutations in mismatch repair genes or by verification of a family history that shows typical features of HNPCC[8–20]. In 1991 the International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC) proposed clinical criteria for HNPCC, the Amsterdam criteria I[21]: (1) colorectal cancer in at least three relatives in at least two generations; (2) one family member diagnosed with colorectal cancer before the age of 50 years; (3) one family member should be a first-degree relative of the other two; and (4) familial adenomatous polyposis should be excluded. These criteria were proposed as a tool for researchers to compare data, but in clinical practice the criteria are often used as a diagnostic guideline. The Amsterdam criteria I were criticized because they did not include extracolonic cancers. New clinical criteria, the Amsterdam criteria II, have therefore been proposed recently by the ICG-HNPCC. These criteria broaden the Amsterdam criteria I by extending the tumour spectrum to endometrial cancer, small bowel cancer, cancer of the ureter and cancer of the renal pelvis[22]. Almost all families that are diagnosed as HNPCC families are identified on the basis of a family history of malignancy.

The aim of this study was to evaluate, in a large prospective population-based study, the accuracy of a suspected HNPCC family history provided by patients with colorectal cancer. Three levels of information were evaluated: knowledge about own previous HNPCC-related malignancy, accuracy of reporting on colorectal cancer among first-degree relatives, and accuracy of reporting on suspected family history of HNPCC.

Patients and methods

The study was designed as a prospective population-based study in four Danish counties with a total population of 1 356 173 on 1 January 1997 (26 per cent of the Danish population). The counties of Aarhus, Ribe, Ringkoebing and Viborg were included successively in the period from 1 November 1995 to 1 August 1997. The inclusion period finished in October 1998. Consecutive eligible patients with colorectal cancer completed a questionnaire concerning malignancy and age at onset among themselves and their relatives.

Questionnaire

Patients were interviewed by their surgeons using a questionnaire concerning their own malignancy, and also malignancy and the age of onset among first-degree relatives (parents, siblings and children). Second-degree relatives were also considered if patients were diagnosed before the age of 50 years or if colorectal cancer was reported among first-degree relatives. All types of cancer were registered, and the doctors completing the questionnaires were asked specifically about primary location. The patients received oral information about the purpose of the study. Written concent was obtained concerning participation, use of hospital information and permission for follow-up contact.

Identification of probands

Probands were identified by the five institutes of pathology in the study area. All patients with colorectal cancer in Denmark are diagnosed and treated within the public healthcare system, which ensured that all patients with colorectal cancer diagnosed within the catchment area were identified. The HNPCC study group received the histology report at the same time as the local surgical department. The databases of the institutes of pathology were checked regularly to ensure that no patients were missed. The study group was therefore able to alert the surgical department each time a patient met the criteria for inclusion. All 16 surgical departments managing patients with colorectal cancer in the study area participated in the study.

Identification of relatives

The questionnaires were used to construct a pedigree for each family. If a patient reported HNPCC-related cancer among family members, efforts were made to identify family members with cancer, and to extend the pedigree whenever possible. The local parish register was contacted if the patient was not able to identify family members. Population registration has been mandatory in Denmark since 1924, and since 1968 all Danish inhabitants have been identified by a unique personal identity number. The Danish population is homogeneous which, combined with a long tradition for registration, makes Denmark an ideal country for family studies.

Verification of diagnosis

Once a family member had been identified, access to the medical file and/or autopsy report was requested. If medical files and/or autopsy reports were not available, information on malignancy was obtained from the Danish Cancer Registry, which holds incidence figures from 1 January 1943. The completeness and accuracy of the Danish Cancer Registry ranges from 95 to 97 per cent[23]. If the Danish Cancer Registry had no information on the family member, the death certificate was accessed. Death certificates on Danish citizens who have died since 1878 are available for research.

Classification of family history

The accuracy of the patients' reports was evaluated for those patients who, according to the original questionnaire, reported a family history belonging to one of the three categories listed in *Table 1*. Families belonging to cate-

Table 1 Clinical criteria for evaluated family histories reported by patients

Category 1	
Amsterdam criteria I	Colorectal cancer in three family members in two successive generations One family member diagnosed before the age of 50 years One family member must be a first-degree relative to the two others Familial adenomatous polyposis excluded
Amsterdam criteria II	As Amsterdam criteria I apart from the inclusion of endometrial cancer, small bowel cancer, cancer of the ureter and cancer of the renal pelvis
Category 2	As Amsterdam criteria I apart from inclusion of cancer of the stomach, biliary tract, urinary tract, ovary, pancreas and unspecified abdominal cancer (category I families excluded)
Category 3 (a and b)	(a) Probands with one first-degree relative with gastrointestinal or urogenital cancer (b) Proband or relative diagnosed before the age of 50 years (category I and II families excluded)

gories 1 and 2 according to the patients were considered as suspected HNPCC, while patients belonging to category 3 were not; however, the latter's family histories were considered relevant for further exploration and were therefore studied in detail.

Results

A total of 1514 patients was diagnosed with primary colorectal cancer in the study period. Among these, 186 were not eligible for various reasons (severe illness, death before inclusion, psychosis, depression, senility, intellectual impairment). Among 1328 eligible patients 1200 (90·4 per cent) completed the questionnaire. Eighty-seven probands (7·3 per cent) reported that their families belonged to category 1, 2 or 3, and these families were the subject of this study.

Knowledge of previous hereditary non-polyposis colorectal cancer-related malignancy

Among 1200 probands, 38 patients (3·2 per cent) reported that they had previously developed at least one HNPCC-related cancer (25 colorectal cancers, 12 endometrial cancers, one stomach cancer). Correct cancer localization was verified in all 38 patients, but in one patient (who had a sarcoma of the uterus) the cancer was not related to HNPCC (true-positive rate 97 per cent). Among the 1200 probands, 40 patients were registered in the Danish Cancer Registry as having previously developed at least one HNPCC-related cancer. Thirty-seven of 40 patients registered with previous HNPCC-related malignancies were reported by the probands (sensitivity 93 per cent). Of the three patients who had not reported previous HNPCC-related malignancy, two had endometrial cancer and one cancer of the ureter.

Colorectal cancer among first-degree relatives

A total of 167 probands (13·9 per cent) reported colorectal cancer among 196 first-degree relatives, 164 of whom (83·7 per cent) were identified from the Danish parish registers. The diagnosis of colorectal cancer was verified in 134 cases (a true-positive rate of 81·7 per cent) (*Table 2*). Among the remaining 30 relatives, six (3·7 per cent) presented with other HNPCC-related cancers. Therefore 140 (85·4 per cent) of 164 identified first-degree relatives had developed an HNPCC-related cancer (*Table 2*). If all 196 first-degree relatives identified by the patients as having colorectal cancer were included in the evaluation, the colorectal cancer verification rate dropped to 68·4 per cent (134 of 196), and the rate of verified HNPCC-related cancers was 71·4 per cent (140 of 196).

Accuracy of a suspected previous family history of hereditary non-polyposis colorectal cancer

A total of 14 probands reported that their families belonged to category 1 (Amsterdam criteria I or II) (*Table 3*). This was confirmed in 11 families (true-positive rate 79 per cent). In two cases, the probands belonged to previously identified HNPCC families. Excluding these two cases, a true-

Table 2 Identified first-degree relatives (n = 164) with colorectal cancer according to the proband

	No. of patients	Verified malignancy	Verified HNPCC-related cancer
True-positive reports of colorectal cancer	134 (81·7)	134 colorectal cancer	134
False-positive reports of colorectal cancer			
HNPCC related	6 (3·7)	1 ovarian cancer	1
		3 stomach cancer	3
		1 gallbladder cancer	1
		1 pancreatic cancer	1
Not HNPCC related	10 (6·1)	4 prostate cancer	
		1 carcinoma of cervix	
		1 vulvar cancer	
		1 bladder cancer	
		1 skin (basal cell carcinoma)	
		2 carcinoma of the anus	
Not site-specific cancer	3 (1·8)	1 unspecified cancer	
		1 metastasis to liver	
		1 metastasis to peritoneum	
No cancer registered	11 (6·7)		
Total	164 (100)	153 (93·3)	140 (85·4)

Values in parentheses are percentages. HNPCC, hereditary non-polyposis colorectal cancer positive history of meeting the Amsterdam criteria I or II was seen in nine of 12 families, giving a true-positive rate in newly identified families of 75 per cent. In three families the Amsterdam criteria I or II were not met (false-positive rate 21 per cent) (*Table 3*).

Verification of the diagnosis in the families belonging to categories 2 and 3 according to the patients permitted another seven families who fulfilled the Amsterdam criteria I or II to be identified. In total 18 patients' family history fulfilled the Amsterdam criteria I or II, but seven of these were not reported by patients, resulting in a false-negative family history in 39 per cent. Exclusion of the two families who belonged to previously identified HNPCC families yielded a rate of false-negative family history of meeting the Amsterdam criteria I or II in 44 per cent (seven of 16 families). In six of the seven false-negative families, the proband had developed the first colorectal cancer before the age of 50 years, and all seven patients reported HNPCC-related malignancy among first-degree relatives.

A total of 24 probands reported that they belonged to category 2 and not category 1 (*Table 3*). In two of these, the proband's family met the Amsterdam criteria I or II after further exploration of the family history. A total of 49 probands reported that they belonged to category 3 and not category 1 or 2 (*Table 3*). Further exploration and verification made it clear that for five patients the family met the Amsterdam criteria I or II.

Discussion

The assessment of a family history of malignancy is crucial to the clinical evaluation of inherited susceptibility to cancer in general and in patients with colorectal cancer. However, no large-scale prospective population studies have yet evaluated the accuracy of patients' reporting of HNPCC-related malignancy among family members. This study has shown that patients with colorectal cancer give reliable information when asked to report on their own previous HNPCC-related malignancies; 93 per cent of the previously developed HNPCC-related cancers were identified simply by asking the patients. The questionnaires were completed by surgeons during an interview, so information about previous malignancies could have been given to the patient during the interview. However, for all practical purposes, an interview is the ideal way of identifying previous HNPCC-related cancer among patients with colorectal cancer. When patients reported colorectal cancer among first-degree relatives, the information was correct in 68·4 per cent of cases (81·7 per cent if non-identified first-degree relatives were excluded) (*Table 2*).

The results of this study suggest that when patients with colorectal cancer report a family history that clinically meets the Amsterdam criteria I or II the information is correct in most cases, but the risk of misclassification is relatively high. The results are comparable to those of Church and McGannon[24], who found that 77 per cent of patients reported accurately when asked about a family history of colorectal cancer. Aitken *et al.*[25] obtained a family history for 237 patients, and confirmed a positive history of colorectal cancer (in one or more relatives) in 77 per cent of families identified.

In this study a total of 21 cases met the Amsterdam criteria I or II according to the patients or after verification (18 verified and three rejected). The reporting from the patients showed false-positive and false-negative rates of meeting the Amsterdam criteria I or II of 21 per cent (three of 14) and 39 per cent (seven of 18) respectively. If surveillance were offered solely to families who met the Amsterdam criteria I or II according to the patients, appropriate endoscopic screening would be offered in only 11 (52 per cent) of the 21 families. Although this example is speculative, it emphasizes the risk of identifying the wrong families for endoscopic screening unless the family histories are verified.

Table 3 Unverified and verified information in 87 families identified by probands

Unverified information*		Verified information		
Category	No. of families	Category 1	Category 2	Other
1	14†	11†	0	Rejected 3
2	24	2	10	Rejected 11 Not verifiable 1
3	49	5‡	2	Rejected 15 Verified and no further family history 11 Not verifiable 16
Total	87†	18†	12	

*Number of families belonging to category 1, 2 or 3 according to the probands' information from the original questionnaire. †Includes two cases from known hereditary non-polyposis colorectal cancer families; ‡one family met the Amsterdam criteria I only on extended pedigree

Verification of family members' diagnosis reported by the patients and further exploration among family members if a family history contains features of HNPCC should be standard procedure in the management of hereditary colorectal cancer. HNPCC should not be rejected as a possible diagnosis just because the Amsterdam criteria I or II are not fulfilled, based on the family history obtained from the patient.

The accuracy of patients' reports of malignancy among relatives has been described by several authors[24–28]. Love *et al.*[27] studied 121 consecutive families referred to a cancer genetics clinic. Thirty-nine of 42 reported colonic cancers among first-degree relatives were confirmed. Sijmons *et al.*[28] studied 120 families from a cancer genetics clinic and reported 89 per cent accuracy. In a case–control study including 125 patients with colorectal cancer, Kerber *et al.*[26] found that 11 of 17 colorectal cancers among first-degree relatives were reported correctly by the patients (sensitivity 65 per cent). These results suggest that the reports from self-referred probands and/or probands in cancer genetics clinics are probably more accurate than the reports from unselected patients with colorectal cancer.

Sijmons *et al.*[28] demonstrated that verification changed clinical management in six of 120 families from a cancer genetics clinic. In five families the genetic risk was found to be reduced. In the present study the proportion of families who changed from one category to another was greater. Moreover, the genetic risk was increased in a large proportion after verification. It is likely that these differences result from the different study designs. Sijmons *et al.*[28] studied families who were selected because positive family histories were reported, while in the present study probands were unprepared and unselected patients with colorectal cancer.

Mutation analysis will probably take over as the most important tool for identifying HNPCC families in the future, but not all families who meet the Amsterdam criteria I or II harbour mutations in the mismatch repair genes. The authors have previously demonstrated that a combination of single-strand conformational polymorphism (SSCP) and heteroduplex analysis is highly efficient in detecting mutations in the major genes *hMLH1* and *hMSH2*[29]. Among the 18 families who met the Amsterdam criteria I or II in this study, *hMLH1*/*hMSH2* mutations were detected in only eight by SSCP and heteroduplex analysis (data not shown)[30]. Furthermore, about 25 per cent of mutation-negative families who meet Amsterdam criteria I, identified among probands with colorectal cancer diagnosed before the age of 50 years, most likely represent coincidental clustering of colorectal cancer among family members[31]. However, mutation-negative families with massive clustering of HNPCC-related cancers should be considered high-risk families. Negative genetic testing does not rule out the possibility of a hereditary colorectal cancer syndrome, and it is therefore important to identify these families and to offer relevant endoscopic screening based on verified family history.

The present study suggests that family studies of HNPCC are not reliable unless the family members' diagnoses are verified from official sources. The study also demonstrates that, if endoscopic screening is offered entirely on the basis of unverified information, there is a risk that a large proportion of the families will not be offered relevant surveillance.

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Diagnosis and prognosis of breast cancer by magnetic resonance spectroscopy of fine-needle aspirates analysed using a statistical classification strategy

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Background: The aim was to develop robust classifiers to analyse magnetic resonance spectroscopy (MRS) data of fine-needle aspirates taken from breast tumours. The resulting data could provide computerized, classification-based diagnosis and prognostic indicators.

Methods: Fine-needle aspirate biopsies obtained at the time of surgery for both benign and malignant breast diseases were analysed by one-dimensional proton MRS at 8·5 Tesla. Diagnostic correlation was performed between the spectra and standard pathology reports, including the presence of vascular invasion by the primary cancer and involvement of the excised axillary lymph nodes.

Results: Malignant tissue was distinguished from benign lesions with an overall accuracy of 93 per cent. From the same spectra, lymph node involvement was predicted with an overall accuracy of 95 per cent, and tumour vascular invasion with an overall accuracy of 94 per cent.

Conclusion: The pathology, nodal involvement and tumour vascular invasion were predicted by computerized statistical classification of the proton MRS spectrum from a fine-needle aspirate biopsy taken from the primary breast lesion.

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Introduction

Cytological assessment of fine-needle aspiration biopsy (FNAB) has a sensitivity ranging from 65 to 98 per cent and specificity ranging from 34 to 100 per cent[1], depending on the skill of the person performing the aspiration and the expertise of the cytopathologist. Clinical evaluation, mammography and aspiration cytology (triple assessment) is undertaken on women presenting with breast lumps in many western countries[2,3], with a reported sensitivity of 77–94 per cent and a specificity of 92–95 per cent[4].

Magnetic resonance spectroscopy (MRS) is a new technology capable of determining the pathology of human tissues[5–13]. It can also identify some pathologies before the disease is morphologically apparent and thus visualized by light microscopy[6,8,13]. Proton MRS can distinguish benign from malignant breast lesions on FNAB by visual inspection of spectral data using choline-containing compounds at 3·25 parts per million (p.p.m.) and creatine-containing compounds at 3·05 p.p.m.[12]. The visual inspection method is limited as it requires the FNAB cellularity to be sufficient to generate spectra with a signal-to-noise ratio (SNR) greater than 10 (*Figs 1* and *2*). Despite this limitation the distinction between malignant and benign lesions was previously achieved with a sensitivity and specificity of 95 and 96 per cent respectively[12]. In this initial study 20 per cent of the spectral data were discarded because low aspirate cellularity yielded inadequate spectral SNRs. Furthermore, of the 50 or more available resonances for inspection[5–13] only two were analysed and so diagnostic and prognostic information in the remaining spectra may have been ignored.

This study incorporated a three-stage, robust, statistical classification strategy (SCS) to assess the entire magnetic resonance (MR) spectrum. The robustness of the method

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The Editors have satisfied themselves that all authors have contributed significantly to this publication

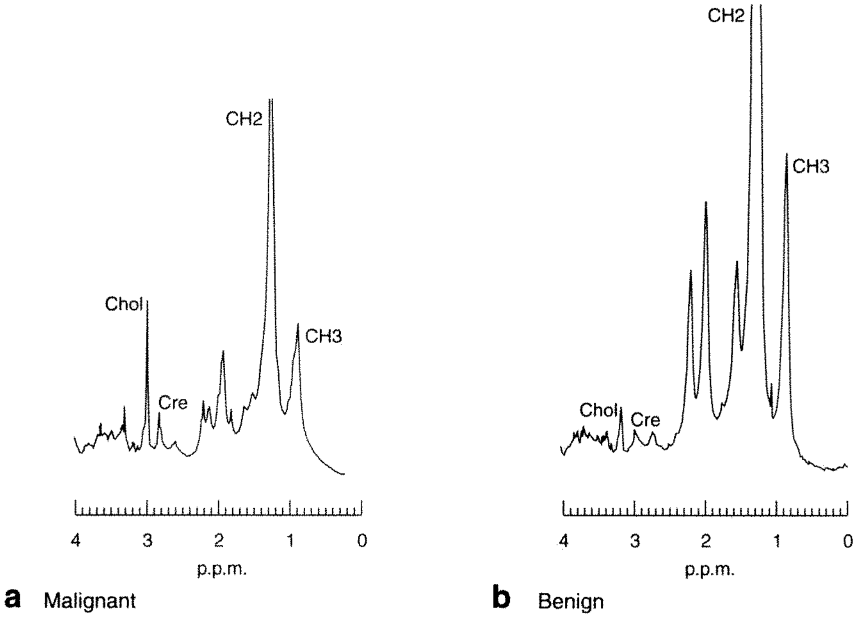

Fig. 1 Proton magnetic resonance spectra (8·5 Tesla) with signal-to-noise ratio above 10 for **a** malignant and **b** benign tumours. A line broadening of 3 Hz was applied to both spectra. The spectra were displayed in absolute intensity mode (noise level similar in both). Chol, choline; Cre, creatine; CH2, methylene; CH3, methyl; p.p.m., parts per million

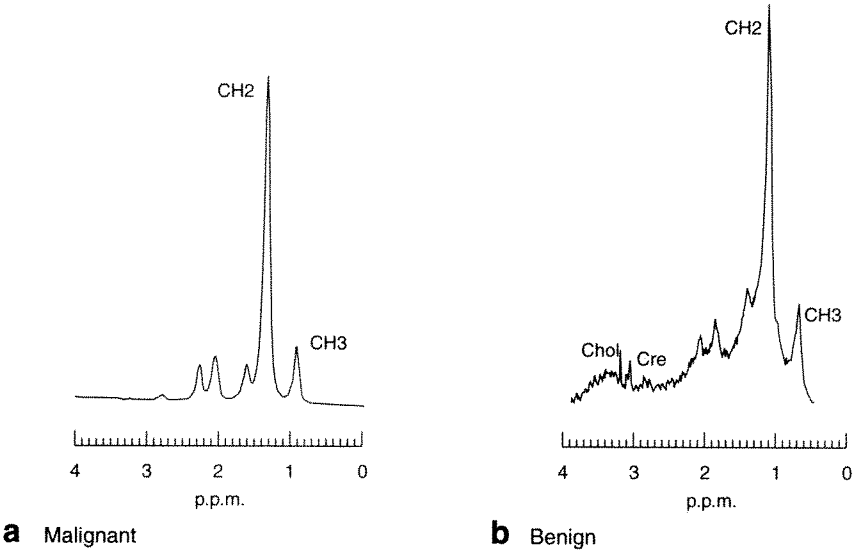

Fig. 2 Proton magnetic resonance spectra (8·5 Tesla) with signal-to-noise ratio below 10 for **a** malignant and **b** benign tumours. A line broadening of 3 Hz was applied to both spectra. The spectra were displayed in absolute intensity mode (noise level similar in both). CH2, methylene; CH3, methyl; Chol, choline; Cre, creatine; p.p.m., parts per million

has been shown with the analysis of proton MR spectra from thyroid[14], ovarian[15], prostate[9] and brain tumours, and tissue specimens[16]. Classifiers have been developed to assess proton MR spectra of breast aspirates against clinicopathological criteria to identify the pathology of samples, including those with suboptimal cellularity and thus SNR, and to ascertain whether other diagnostic and prognostic information is available.

Patients and methods

Patients and specimen collection

An intraoperative FNAB was taken from each patient undergoing breast biopsy by one of three surgeons in separate hospitals between January 1994 and July 1999. Impalpable breast lesions localized by carbon track or hook wire were included, except when the lesion was not palpable at operation or when the histopathological assessment of the specimen could have been compromised. All FNABs were taken during the operation under direct vision. Before the needle was removed from the lesion a tissue sample including the needle track was excised for comparative histopathological study.

The breast lesion was excised *in vivo* via the margin with the greatest apparent depth of normal tissue to ensure that the pathologist could report upon the lesion according to a standard protocol[17]. The specimens were oriented with sutures and radio-opaque vascular clips. The FNAB samples were collected using a 23-G needle on a 5-ml syringe. The number of needle passes and the quality of the aspirate were recorded as well as relevant clinical, investigative and operative details, and the extent of breast and axillary surgery.

Specimen storage and preparation for magnetic resonance spectroscopy

Following complete excision of the breast lesions the FNAB and specimens of tissue excised from around the needle track were placed in polypropylene vials containing 300 µl phosphate-buffered saline (PBS) in deuterium oxide. All specimens were immediately frozen in liquid nitrogen and stored at – 70°C for up to 6 weeks.

For proton MRS, each FNAB specimen was thawed and transferred directly to a 5-mm MRS tube. The volume was adjusted to 300 µl with PBS–deuterium oxide where necessary. Proton MRS assessment of all specimens was performed without knowledge of the correlative histopathological findings.

Magnetic resonance spectroscopy data acquisition and preparation

MRS experiments were carried out on a Bruker Avance™ 360 (Bruker Analytik, Rheinstetten, Germany) wide-bore spectrometer (operating at 8·5 Tesla) equipped with a standard 5-mm inverse detection ^{1}H, ^{13}C probe head. The sample was spun at 20 Hz and the temperature maintained at 37°C. The residual water signal was suppressed by selective gated irradiation. The chemical shifts of resonances were referenced to aqueous sodium 3-(trimethylsilyl)-propanesulphonate at 0·00 p.p.m. or internal remaining water at 4·65 p.p.m. One-dimensional spectra were acquired over a spectral width of 3597 Hz (10·0 p.p.m.) using a 90° pulse of 6·5–7 µs, 8192 data points, 256 accumulations and a relaxation delay of 2·00 s, resulting in a pulse repetition time of 3·14 s. SNR was determined using the Bruker standard software (XWINNMR). The noise region was defined between 8·5 and 9·5 p.p.m. The signal region was defined between 2·8 and 3·5 p.p.m. MRS data were prepared for statistical analysis using in-house software XPREP (Institute for Biodiagnostics, National Research Council of Canada, Winnipeg, Canada). Magnitude spectra consisted of 4000 data points over the spectral width of 10 p.p.m. This region was reduced to 1400 points between 0·4 and 3·9 p.p.m., and the spectra were normalized to the total integral in this region.

Histopathology

Diagnostic correlation was obtained by comparing spectral analysis with the pathology report which provided information on the tumour and axillary lymph nodes. Lymph nodes were embedded and sectioned according to standard protocols.

Cytological analysis of the FNAB after MRS was not possible because cellular detail had been compromised by autolytic changes. Instead, FNAB sampling accuracy was verified by a separate histopathological assessment by a single pathologist of tissue removed from the aspiration site of the MRS sample. Tissue specimens were thawed, fixed in formalin–acetic acid–alcohol, embedded in paraffin, sectioned at 7 µm, stained with haematoxylin and eosin according to standard protocols, and reviewed under the light microscope by the pathologist, who did not have access to the clinical or MRS data. Tissue preservation, abundance of epithelial cells relative to stroma, and presence of potentially confounding factors such as fat and inflammatory cell content were reported in addition to the principal diagnosis.

Statistical classification strategy

A three-stage classification strategy[18] was employed to analyse the MRS data. The SCS strategy was designed specifically for MR and infrared spectra of biofluids and tissue biopsies, the databases of which contain many fewer spectra than the number of data points (attributes) in each spectrum. The strategy consisted of three stages. First the MR magnitude spectra were preprocessed (in order to

Table 1a Magnetic resonance spectroscopic comparison of malignant *versus* benign breast lumps: visual inspection

	Sensitivity (%)	Specificity (%)
All spectra (*n* = 140)		
Malignant (*n* = 83) *versus* benign (*n* = 57)	85	82
Spectra with SNR > 10 (*n* = 109)		
Malignant (*n* = 60) *versus* benign (*n* = 49)	100	87

SNR, signal-to-noise ratio

Table 1b Magnetic resonance spectroscopic comparison of all malignant ($n = 83$) *versus* benign ($n = 57$) breast lumps: statistical classification strategy

	Benign	Malignant	Sensitivity (%)	Specificity (%)	PPV (%)	Crisp (%)
Benign	51	4	93	92	89	96
Malignant	6	73	92	93	95	95

Overall accuracy 93 per cent (excluding six fuzzy samples); overall proportion crisp 96 per cent (134 of 140). A class assignment was fuzzy if the class probability was less than 75 per cent. PPV, positive predictive value

Table 1c Magnetic resonance spectroscopic comparison of malignant ($n = 60$) *versus* benign ($n = 49$) breast lumps with signal-to-noise ratio above 10: statistical classification strategy

	Benign	Malignant	Sensitivity (%)	Specificity (%)	PPV (%)	Crisp (%)
Benign	46	3	94	98	98	100
Malignant	1	58	98	94	95	98

Overall accuracy 96 per cent (excluding one fuzzy sample); overall proportion crisp 99 per cent (108 of 109). A class assignment was fuzzy if the class probability was less than 75 per cent. PPV, positive predictive value

eliminate redundant information and/or noise) by submitting them to a genetic algorithm-based optimal region selection (GA_ORS)[19] which finds a few (at most five to ten) maximally discriminatory subregions in the spectra. The averages in these subregions are the ultimate features and were used at the second stage. The second stage used the features found by GA_ORS to develop linear discriminant analysis (LDA) classifiers that were made robust by an in-house (Institute for Biodiagnostics, National Research Council of Canada) bootstrap-based cross-validation method[20]. The cross-validation approach proceeded by randomly selecting about half of the spectra from each class and using these to train a classifier (LDA). The resulting classifier was then used to validate the remaining half. This process was repeated 1000 times (with random replacement), and the optimized LDA coefficients were saved. The weighted average of these 1000 sets of coefficients produced the final classifier. The ultimate classifier was the weighted output of the 1000 different bootstrap classifier coefficient sets and was designed to be used in a clinical setting as the single best classifier. The classifier yielded probabilities of class assignment for the individual spectra. For particularly difficult classification problems the third stage was activated. This aggregated the outputs (class probabilities) of two independent classifiers to form a computerized consensus diagnosis (CCD)[14,16]. The consequence of CCD is that classification accuracy and reliability are generally better than for the best of the individual classifiers.

Results

Benign *versus* malignant

Proton MR spectra were recorded for FNABs (irrespective of the cellularity of the aspirate) from 140 patients. The age range of the patients was 20–90 (mean(s.d.) 54·7(5·0)) years. Visual inspection of the 83 malignant and 57 benign spectra (including 31 spectra with a SNR of less than 10 in the region 2·8–3·5 p.p.m.) gave a sensitivity and specificity of 85 and 82 per cent respectively for the diagnosis of malignancy (*Table 1a*) based on the ratio of MR signals from creatine (3·05 p.p.m.) and choline (3·25 p.p.m.). When SCS-based classifiers were developed for this database (*Table 1b*), 96 per cent of the 140 spectra could be assigned unambiguously and crisply by the classifier as malignant or benign. Class assignments were crisp if class probabilities were greater than 75 per cent. The sensitivity and specificity were 93 and 92 per cent respectively. When the 31 spectra with a poor SNR were removed from the SCS database (*Table 1c*) a sensitivity and specificity of 94 and 98 per cent respectively, and an overall crispness of 99 per cent, were obtained.

Lymph node involvement

A separate SCS-based classifier was generated for lymph node involvement. MR spectra from 29 patients with breast cancer with nodal involvement and from 32 without nodal involvement were subjected to SCS analysis. The age range of the patients was 29–85 (mean(s.d.) 58·4(13·1)) years. The number of axillary nodes sampled for each patient ranged between 1 and 34 (mean(s.d.) 13·8(7·2)) nodes . The presence of lymph node metastases was predicted by SCS with a sensitivity of 97 per cent and a specificity of 96 per cent (*Table 2a*). The overall crispness of the data was 95 per cent, i.e. three of the 61 samples were classified as fuzzy (class probability less than 75 per cent). An overall 95 per

Table 2a Prognostic indicators using statistical classification strategy: lymph node involvement (present in 29 of 61 tumours)

	Present	Absent	Sensitivity (%)	Specificity (%)	PPV (%)	Crisp (%)
Present	25	1	96	94	93	90
Absent	2	30	94	96	97	100

Overall accuracy 95 per cent (excluding three fuzzy samples); overall proportion crisp 95 per cent (58 of 61). A class assignment was fuzzy if the class probability was less than 75 per cent. PPV, positive predictive value

Table 2b Prognostic indicators using statistical classification strategy: vascular invasion (present in 33 of 85 tumours)

	Present	Absent	Sensitivity (%)	Specificity (%)	PPV (%)	Crisp (%)
Present	26	5	84	100	100	94
Absent	0	49	100	84	90	94

Overall accuracy 94 per cent (excluding five fuzzy samples); overall proportion crisp 94 per cent (80 of 85). A class assignment was fuzzy if the class probability was less than 75 per cent. PPV, positive predictive value

cent accuracy for the test was obtained when specimens classified as fuzzy were excluded.

Vascular invasion

A separate SCS classifier was generated for vascular invasion. MR spectra from 33 patients with breast cancer with vascular invasion and 52 without were subjected to SCS analysis. The age range of the patients was 29–101 (mean(s.d.) 60·6(14·3)) years. The presence of vascular invasion was predicted by SCS with a sensitivity of 84 per cent and specificity of 100 per cent (*Table 2b*). The overall crispness of the data was 94 per cent, i.e. five of the 85 samples were classified as fuzzy (class probability less than 75 per cent). An overall 94 per cent accuracy for the test was obtained when specimens classified as fuzzy were excluded.

Discussion

MRS can monitor biochemical changes, including those related to cellular proliferation and cell surface fucosylation, that continue to occur throughout tumour development and progression[21–24]. However, when information from large numbers of individual patients is involved, visual inspection of MRS data may prove less than optimal for extracting all diagnostic and prognostic information owing to the continuum of spectral changes during tumour development and progression that are being recorded simultaneously.

MRS has proven accurate in its ability to assess cancers in many organs[5–13]. Breast tissue proved elusive until the strong lipid signal was removed by recording MRS data from a fine-needle aspirate rather than a tissue biopsy[12]. Visual inspection of MR data from FNAB of breast lesions has been reported to diagnose malignancy with a sensitivity and specificity of 95 and 96 per cent respectively. The method is, however, accurate only when the SNR of the MR spectra (2·8–3·5 p.p.m.) is greater than 10. This is a feature of the number of cells in the aspirate. In a clinical setting, aspirating sufficient cells to achieve a SNR above 10 is not always possible.

The introduction of SCS analysis of the data, which includes preprocessing of the raw MR data and subsequent computerized classification, has allowed a more robust method for the diagnosis of breast disease from a FNAB from the primary lesion than was possible with visual inspection analysis. Visual analysis relies upon a SNR that allows unequivocal determination of resonance intensities at those frequencies known to be diagnostic, i.e. choline (3·25 p.p.m.) and creatine (3·05 p.p.m.)[12]. Using objective SCS-derived classifiers, all data points in each spectrum were available for examination. It was then possible to distinguish malignant from benign pathologies for spectra from all FNAB, including those with low SNR, with a higher sensitivity and specificity (93 and 92 per cent respectively; *Table 1b*) than was achieved using visual inspection methods (85 and 81 per cent respectively; *Table 1a*). That SCS-based analysis could more reliably classify a greater proportion of spectra than could be assessed visually is testament to the robustness and greater generality of the computer-based approach. The specificity of the SCS-based diagnosis is further improved by presenting spectral data with high SNR to the computer. The improvement in specificity gained for spectra with sufficient SNR (*Table 1c*) suggests that the quality and cellularity of the aspirate, and so the aspiration technique, are important.

Using SCS to train classifiers to recognize patterns containing more complex information that is not visually obvious has allowed prediction of lymph node involvement with an accuracy of 95 per cent, and vascular invasion with an accuracy of 94 per cent. This emphasizes the wealth of chemical information that is available from the MR spectrum of a FNAB of a breast lesion and that can be extracted with the appropriate statistical approach (*Table 2a*).

There was considerable overlap between the large number of spectral regions selected by GA_ORS and used to develop the respective classifiers. This large number of regions indicates that many metabolites may have contributed to the success of the SCS. It was not possible to identify particular metabolites of key diagnostic importance, as most regions identify frequency ranges that may include a large number of compounds.

A major challenge in breast cancer is the need to identify and understand the factors that most affect a patient's prognosis. The best indicator of survival for patients with early breast cancer is still axillary lymph node status[25–28]. MRS can predict nodal involvement from the cellular material derived solely from the primary tumour.

The power, speed and reproducibility of a computer-based diagnosis suggests that classifiers could supplant the human observer in the clinical laboratory. However, quality control issues are of importance. The MRS method was successful with cells aspirated from the breast but not on core biopsies that contained a high level of fat which masked diagnostic and prognostic information. The mechanical aspiration of the sampling procedure causes the fat to disassociate, leaving cells in suspension.

Sample handling is of utmost importance if the specimen is not to be degraded. Care must be taken in freezing, storage and thawing of the specimen, as well as with maintaining constant MR spectrometer acquisition parameters. The magnetic field strength at which this database was collected was 8·5 Tesla (360 MHz for proton) and it must be emphasized that some spectral patterns are frequency dependent. Degradation of the sample during the analysis is not limiting because the test is rapid, taking no more than 12 min to collect the MR data.

Finally, unless the clinical and pathology databases used to train the classifier are representative of the full range of pathologies and the complete demographics of the population, the classifier will be inadequately prepared for all the possibilities it might encounter in clinical practice. The method is now being evaluated further with a large number of tumours and by analysing specimens collected through the skin before surgery. If the technique can be applicable as an additional procedure alongside triple assessment then it could have significant clinical value.

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Original article

Pattern of cervical lymph node metastases from papillary carcinoma of the thyroid

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Introduction: The management of cervical metastases from papillary thyroid carcinoma ranges from selective removal (berry picking) to a formal comprehensive neck dissection. Without a clear understanding of the distribution of nodes at risk, the formulation of strategies on how best to manage the clinically positive neck is difficult. This study reports on observations made in patients who underwent a therapeutic comprehensive neck dissection for metastatic papillary thyroid carcinoma by defining lymph node involvement with respect to neck level.

Methods: The clinical records and pathological reports of 75 consecutive patients who underwent a neck dissection for cervical metastases from papillary thyroid carcinoma over a 10-year period were reviewed. All dissections were therapeutic in nature, being performed in patients with clinically positive neck nodes. Eighty neck dissection specimens were obtained and analyses were divided into three groups by virtue of the type of dissection performed: a bilateral comprehensive neck dissection, unilateral radical neck dissection and unilateral comprehensive neck dissection. The relative involvement of cervical nodes was analysed with reference to node levels I–V.

Results: Patients in the anterolateral group (levels II, III and IV) were at greatest risk of metastatic disease, with level III nodes consistently the most frequently involved, across all treatment groups. Only three patients exhibited level I involvement, all of whom had extensive neck disease involving all or almost all neck levels.

Conclusion: The majority of patients present with multiple level node disease, with the anterolateral group at greatest risk. A comprehensive neck dissection is recommended for all patients with palpable cervical lymphadenopathy.

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Introduction

The first site of metastasis from papillary thyroid carcinoma is the regional node basins of the central and lateral neck[1]. A previous study found occult metastases in the central compartment in 35 per cent of patients subjected to elective tracheo-oesophageal groove (TEG) clearance[2]. Occult metastases to the lateral cervical nodes are found in 38–90 per cent of patients without cervical lymphadenopathy clinically[1,3]. Substantial evidence exists that cervical lymph node metastasis does not adversely influence survival in low-risk patients[4–8].

Controversy still surrounds this issue, however, and several studies have reported otherwise[9–11]. Differences also exist regarding the procedure of choice for addressing the neck in papillary thyroid cancer, from a prophylactic neck dissection in a clinically negative neck[12,13] to selective removal (berry picking)[4,14,15] or a formal comprehensive dissection of all lateral neck nodes (comprehensive neck dissection)[10,12,16,17] in a clinically positive neck. Literature on the pattern of lymph node metastasis from papillary thyroid carcinoma is limited and, without a clear understanding of the distribution of nodes at risk, the formulation of strategies on how best to manage a clinically positive neck would be difficult.

Two papers have previously reported on the distribution of cervical metastases from papillary thyroid carcinoma[1,18], but none to date has described papillary nodal metastases by neck level, as has been done so elegantly for squamous cancers of the upper aerodigestive tract by Lindberg[19], Shah[20] and others. To address this issue a retrospective analysis of patients who underwent a therapeutic comprehensive neck dissection for lateral neck disease from papillary thyroid carcinoma was conducted, and lymph node involvement was reported with respect to neck level.

Patients and methods

From June 1988 to March 1999, 75 patients underwent 85 neck dissections for papillary thyroid carcinoma with cervical metastases. A review of the clinical records and pathological reports was conducted to ascertain the prevalence and distribution of cervical metastases by neck level.

Lymph nodes were defined by neck level following the nomenclature proposed by the Memorial Sloan-Kettering Cancer Center in the USA, with level I representing submental and submandibular groups, levels II, III and IV representing upper, mid and lower jugular groups respectively, and level V posterior triangle nodes[21]. The node levels on the dissected specimen were marked individually by the surgeon with sutures of various lengths for identification by the pathologist (*Fig. 1*). Data from five patients had to be excluded because of incomplete histological reporting, leaving 70 patients from whom 80 neck dissection specimens were obtained and analysed.

All neck dissections were therapeutic in nature, in what was deemed to be a clinically positive neck at the time of operation. A clinically positive neck was defined as palpable cervical lymphadenopathy, regardless of any additional imaging used for further evaluation.

A comprehensive neck dissection involving complete removal of lateral neck nodes from level I to level V was performed in all patients. In 57 cases, the spinal accessory nerve, internal jugular vein and sternomastoid were preserved (comprehensive type III dissection), while in 18 patients sacrifice of one or more of these structures was required. Classical radical neck dissections were performed for patients with extensive locoregional disease with either extrathyroidal or extranodal spread. Bilateral neck dissections were performed in patients who exhibited bilateral nodal involvement clinically.

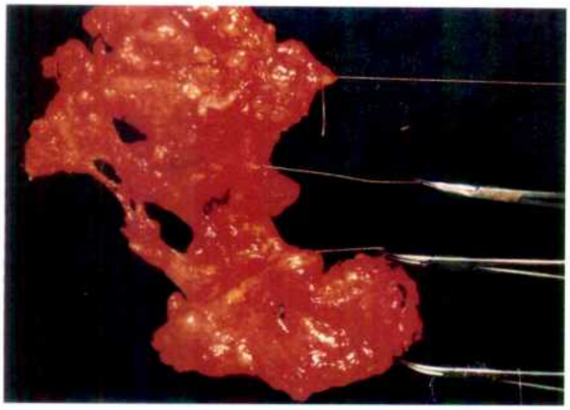


Fig. 1 Node levels on a neck dissection specimen of papillary thyroid carcinoma marked with sutures of various lengths for identification by the pathologist

Analysis of tracheo-oesophageal node involvement was not included as this issue has been addressed by a separate study[2]. Patients were considered to have a positive level when one or more nodes in the particular level were reported to contain tumour.

Results

The study group of 70 patients comprised 49 women (70 per cent) and 21 men. The age range was 23–83 (mean 41) years. Fifty-nine patients (84 per cent) had a total thyroidectomy, and the remaining 11 underwent unilateral total lobectomy with isthmusectomy. Fifty-three patients (76 per cent) had the thyroidectomy and neck dissection at the same sitting, while 17 (24 per cent) had a metachronous dissection (i.e. neck dissection performed at a later date when the patient had developed clinically positive neck nodes on subsequent follow-up).

Analyses of the 80 neck dissection specimens were divided into three groups by virtue of the type of dissection performed. Group 1 involved patients who underwent bilateral comprehensive neck dissections, patients in group 2 had a unilateral classical radical neck dissection, and those in group 3 underwent a unilateral comprehensive neck dissection with preservation of the three neck structures mentioned above. The analyses were stratified into groups for comparison and to exclude bias based on the nature of the dissection performed. The distribution of specimens according to the groups is given in *Table 1*.

The prevalence and distribution of the histologically confirmed cervical metastases was analysed for the three groups with respect to neck level (*Table 2*; *Fig. 2*). In group 1, of a total of 20 specimens obtained from ten patients, 14 exhibited level III involvement, and 12 had level IV and nine had level II involvement. In group 2, of a total of 18 specimens, 13 had level III involvement, and 12 and ten had level IV and II involvement respectively. In group 3, with 42 specimens, 25 showed level III involvement, with 21 and 20 having level IV and II involvement respectively. Each group had only one specimen containing disease in level I. These

Table 1 Type of neck dissection

Group	Type of dissection	No. of specimens
1	Bilateral comprehensive	20 (25)
2	Unilateral classical radical	18 (22)
3	Unilateral comprehensive	42 (52)

Values in parentheses are percentages

specimens with level I involvement all had extensive nodal disease; two exhibited involvement of all five levels and one had all levels except for level IV. Level V nodes were never found to be involved in isolation, and were most commonly involved in association with level III and IV disease.

Sixty-six specimens (82 per cent) exhibited nodal disease at multiple levels. Of the 14 specimens with single-level disease only, six had disease in level III, five showed level IV involvement and three had level II involvement. Nine of these 14 specimens exhibited only a single positive node within the involved level. The mean number of positive nodes in those with single-level involvement was 2·2, compared with 3·2 in those with multi-level disease. The mean number of nodes removed from each of the groups 1, 2 and 3 was 20·7, 21·9 and 21·5 respectively.

The results show that, irrespective of the type of neck dissection performed, the anterolateral nodes (levels II, III and IV) were at greatest risk of metastatic disease. Within the anterolateral chain, level III nodes were consistently the most frequently involved, followed by level IV and then level II nodes. The nodes at risk were similar in patients with single or multiple level involvement, reflecting that disease burden *per se* did not significantly affect the pattern distribution of metastatic disease to the lateral neck. Level V nodes were less frequently involved, and level I nodes were seen only in those with extensive neck disease.

Table 2 Nodal metastases by neck level

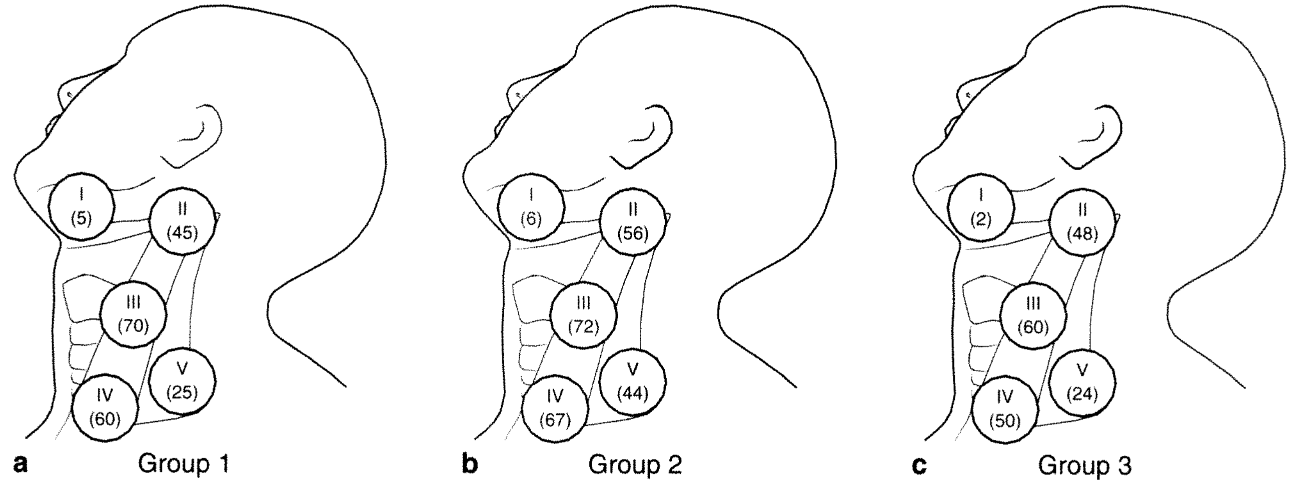
Neck level	Group 1 (n = 20)	Group 2 (n = 18)	Group 3 (n = 42)
I	1	1	1
II	9	10	20
III	14	13	25
IV	12	12	21
V	5	8	10

Discussion

The prognostic value of neck metastases, as well as the necessity for a formal therapeutic lateral neck dissection *versus* selective node removal in a clinically positive neck, is still controversial. There is little doubt that some form of neck dissection is indicated in patients with palpable cervical lymphadenopathy, and should include nodes at greatest risk.

Analyses from this series of patients yield the following observations. The majority of patients (82 per cent) with lateral neck disease present with multiple-level nodal involvement. The anterolateral group of nodes (levels II, III and IV) is at greatest risk of metastatic disease, with level III nodes being the most frequently involved. This pattern distribution is consistent across all dissection groups. Level I and V nodes were never found to be involved in isolation, but always in association with disease at multiple levels. Level I involvement was rare (4 per cent) and was always associated with extensive neck disease. Finally, patients with single- or multiple-level disease showed a similar pattern of distribution of involvement of lateral neck nodes (levels III, IV and II in decreasing order of frequency).

Two other papers have previously reported findings on lymph node metastases from papillary thyroid carcinoma. Noguchi *et al.*[1] used a different lymph node classification system but found that metastases occur first to the



a Group 1 **b** Group 2 **c** Group 3

Fig. 2 Nodal metastases by neck level (I–V) in the three groups: group 1, bilateral comprehensive dissection (20 specimens); group 2, unilateral classical radical (n = 18); group 3, unilateral comprehensive (n = 42). Values in parentheses indicate the percentage of specimens in each group with that level of involvement

paratracheal (TEG) nodes and metastasis to the neck follows a similar distribution. Gimm *et al.*[18] reported their data by yet another lymph node compartment classification, by dividing metastases into cervicocentral and cervicolateral groups. This report is the first detailing lymph node metastases by defining involvement with respect to neck level. It is noteworthy that in squamous cancers of the upper aerodigestive tract, Shah[20,21] found that the anterolateral group of nodes is also most frequently involved in tumours that arise from the same anatomical subregion (i.e. oropharynx, hypopharynx and larynx).

Increased recurrence rates, with no difference in survival, have been reported by Mazzaferri[23], Hubert *et al.*[24] and Hughes *et al.*[8]. Several studies, however, have reported a significant decrease in survival in patients with positive nodes[9,25].

As a large proportion of patients with lateral neck disease harbour multi-level involvement, the optimal procedure for patients with palpable cervical lymphadenopathy from papillary thyroid carcinoma should be a formal comprehensive neck dissection. This is also the practice of other centres[10,12,16,17] as it ensures complete clearance of all lateral neck disease and can be performed with minimum morbidity if all the vital neck structures are preserved. Further, as level I and V nodes were never found to be involved in isolation, and are often reflective of more extensive disease, a comprehensive removal of all nodes should be undertaken, despite the fact that these may be the only levels that are clinically palpable.

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Original article

Intragastric balloon in the treatment of patients with morbid obesity

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Background: Morbid obesity is a major health problem. This study evaluated the effectiveness and safety of an intragastric balloon (IGB) for the treatment of morbid obesity.

Methods: Sixty-nine IGBs were inserted endoscopically over a 3-year period in 63 consecutive patients (59 women; median age 41 (range 24–67) years). Median weight and body mass index were 124·5 (range 89·0–177·8) kg and 46·3 (range 36·2–72·4) kg/m^2 respectively. Significant coexistent disease was present in 34 patients. Median American Society of Anesthesiologists score was 3 (range 1–4). Data were recorded following retrospective review of patient case notes.

Results: Mean operating time was 22 (range 15–30) min and median inpatient stay was 1 (range 1–6) day. Vomiting was the commonest early complication following 31 procedures and necessitated early removal of four IGBs. Of 58 patients with long-term follow-up, 18 suffered displacement of the IGB after at least 6 months *in situ* and three required a laparotomy for intestinal obstruction. Fifty patients (86 per cent) lost weight; median weight loss was 15·0 kg ($P < 0·001$). Median excess weight loss was 16·4 (range − 49·0 to + 4·8) and 18·7 (range − 51·5 to 12·6) per cent by 4 and 7 months after IGB insertion respectively.

Conclusion: The IGB represents a useful device for the treatment of morbid obesity, particularly in preparation for definitive antiobesity procedures. Early IGB replacement is essential to minimize complications.

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Introduction

Obesity represents a major health and socioeconomic problem which results in a significant reduction in quality of life. Morbid obesity is associated with an increase in sleep apnoea[1], non-insulin-dependent diabetes mellitus[2], hypertension[3], ischaemic heart disease[4], gallstones[5], lipid disorders[6], degenerative joint disease[7] and certain cancers[8]. Treatment remains challenging but when successful results in a substantial improvement in co-morbidity and prolonged life expectancy[9,10]. Conservative measures including dieting, behavioural modification and appetite suppressants are rarely successful. A number of surgical antiobesity procedures have been developed although some, including jejunoileal bypass surgery, have been abandoned owing to severe complications and late deaths[11]. Alternative procedures, including vertical or horizontal banded gastroplasty[12,13], gastric bypass[14] and open insertion of adjustable gastric bands[15], have remained popular but are still associated with significant morbidity[13,16] and death in some series[17]. This has driven the development of minimally invasive procedures for morbid obesity.

Intragastric balloons (IGBs) have been used in the past in an attempt to induce early satiety which, together with an effective exercise programme and dietary modification, results in weight loss which theoretically should be maintained with behavioural modification. The Bioenterics IGB (BIB®; Bioenterics Corporation, Carpinteria, California, USA) is a silicone elastic balloon with a self-sealing radio-opaque valve which is placed in the stomach endoscopically and inflated under direct vision. The authors' 3-year experience using this new IGB for the treatment of morbid obesity is presented.

Patients and methods

Sixty-three consecutive patients who had insertion of an IGB for morbid obesity between 1997 and 2000 were studied. Six patients had two consecutive balloons inserted. Morbid obesity was defined as a body mass index (BMI) greater than 40 kg/m^2. Ideal body-weight was calculated assuming an ideal BMI of 23 kg/m^2. All patients had been obese for a minimum of 5 years, had failed conservative treatment and had no major psychiatric disorder or alcoholism. Patients were screened for major endocrine disorders and were referred to a dietician. Consent was obtained only after discussion of the principal risks and adverse effects of the IGB.

All IGBs were inserted under general anaesthesia by a single surgeon (M.H.S.) following routine oesophagogastroscopy to exclude peptic ulceration or a large hiatus hernia which would preclude insertion of the balloon. Following balloon placement into the body of the stomach, the device was inflated under direct vision using normal saline stained with methylene blue, which would alert the patient to unexpected deflation of the balloon. Once able to tolerate fluids by mouth, patients were discharged from hospital on a regular proton pump inhibitor with hyoscine butylbromide and antiemetics as required.

Patients were assessed in the outpatient clinic every 6–8 weeks. Data were recorded on a preprinted standard sheet following retrospective review of patient case notes. Data were analysed using one-way analysis of variance and statistical significance was set at $P < 0{\cdot}05$.

Results

Patient demographics

There were 59 women and four men with a median age of 41 (range 24–67) years. Two patients had previously undergone vertical banded gastroplasty but had suffered staple line disruption. All patients had been obese for at least 5 years and conservative treatments, including dieting, jaw wiring, appetite suppressants, acupuncture and behavioural therapy, had failed. Some 34 patients had significant coexistent medical disease including hypertension in 13, angina in four, asthma or chronic obstructive airway disease in 13, non-insulin-dependent diabetes in four, hypercholesterolaemia in two and myocardial infarction in two of 63 patients. Five patients had hypothyroidism but were biochemically euthyroid on treatment.

Insertion of the intragastric balloon

There were no contraindications to balloon insertion in any patient. Balloons were inflated to a median volume of 590 (range 420–750) ml. Median weight and BMI at operation were 124·5 (range 89·0–177·8) kg and 46·3 (range 36·2–72·4) kg/m^2 respectively. Median American Society of Anesthesiologists score was 3 (range 1–4), mean operating time was 22 (range 15–30) min and median inpatient stay was 1 (range 1–6) day.

Mortality and morbidity

The commonest early complications were nausea and/or vomiting in 31 and abdominal pain in ten patients. Vomiting was managed with nil by mouth, intravenous fluids, metoclopramide and ondansetron, and usually settled over a few days. Four IGBs were associated with intractable vomiting, with dehydration and hypokalaemia in one patient. All required early removal within 3 weeks of placement. Two patients complained of diarrhoea. Perioperative anaesthetic problems were encountered in one patient who required reintubation and treatment with Doxapram before successful extubation. Long-term morbidity data were available for 56 (92 per cent) of 61 eligible patients. The most significant late complication was deflation and/or displacement of the balloon in 18 patients, but this only occurred when a balloon had been *in situ* for at least 6 months. In these 18 patients, four IGBs became impacted within the gastrointestinal tract. The balloon eventually passed spontaneously through the rectum in one patient while the remaining three patients presented with acute intestinal obstruction due to impaction of the balloon in the terminal ileum ($n = 2$) or sigmoid colon ($n = 1$) necessitating a laparotomy. All made a satisfactory postoperative recovery. The remaining 14 IGBs that became displaced passed spontaneously through the rectum ($n = 12$) or were vomited ($n = 2$). One patient had a stroke 3 months after IGB insertion but the operative mortality rate was zero.

Weight loss

Detailed follow-up weight measurements were available for 58 patients (92 per cent). Fifty patients (86 per cent) had a reduction in pretreatment weight; seven, including two who could not tolerate the balloon, had no weight loss and one gained weight. Median weight reduced from 124·5 (range 89·0–177·8) to 109·5 (range 66·7–171·5) kg during treatment with the IGB ($P < 0{\cdot}001$). Maximal weight loss occurred within the first few months, with a median loss of 16·4 (range −49·0 to +4·8) and 18·7 (range −51·5 to +12·6) per cent of excess body-weight by 4 and 7 months respectively (*Fig. 1*). Two of the six patients who had a second balloon achieved a further small reduction in weight. There was no correlation between balloon volume and weight loss or between pretreatment BMI or body-weight and percentage excess weight loss.

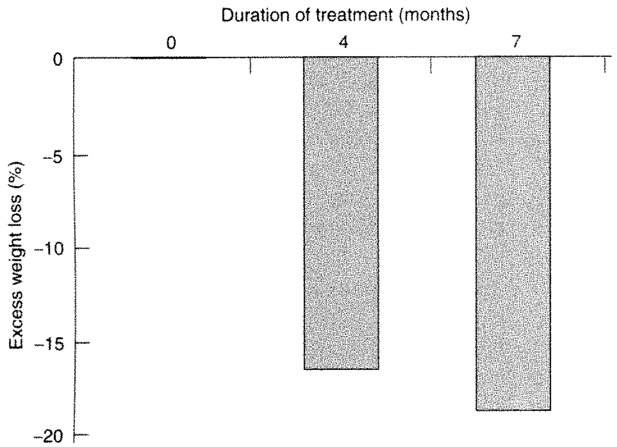

Fig. 1 Percentage excess weight loss during treatment with the intragastric balloon. $P < 0.001$ (one-way analysis of variance)

Balloon removal

Most patients had uneventful endoscopic deflation and removal of the IGB. Problems were encountered in four patients in whom the device could not be removed endoscopically but all balloons eventually passed rectally without complication.

Discussion

IGB therapy resulted in weight loss of around 15·0 kg for most patients. In this study, maximal weight loss occurred within the first few months, after which weight reached a plateau in most patients. A recent study from the USA reported similar findings[18]. However, the IGB has limitations as a therapy for morbid obesity. Despite the initial weight loss, most studies have shown that weight loss reverses following balloon removal, an observation also made by the present authors. In general, the IGB is not useful when used alone despite dieting, exercise and behavioural modification, and must be combined with a definitive antiobesity procedure to achieve long-term weight loss.

A reduction in BMI is desirable before embarking on definitive antiobesity procedures to reduce operative risk, which is closely related to the degree of obesity. Six of the present patients have subsequently undergone laparoscopic gastric banding (LAGB) following successful balloon therapy and a further four are on the waiting list for this procedure. Weiner *et al.*[18] reported a mean weight loss of 18·1 kg after IGB therapy for a median of 16·8 weeks in 15 superobese patients. After balloon therapy, 13 underwent successful LAGB with only one balloon dysfunction. Similarly, IGBs have been used to reduce weight and therefore operative risk in morbidly obese patients undergoing elective joint arthroplasty[19].

Several complications were associated with early designs of IGB including peptic ulceration, gastrointestinal haemorrhage, acute pancreatitis and spontaneous balloon deflation[20–22]. Oesophageal perforation during IGB deployment has been reported[23] but should now be a rare problem as newer balloons are inflated under direct vision. The most serious complication is balloon displacement resulting in intestinal obstruction. Experience using the Garren Edwards gastric bubble demonstrated that balloon failure typically occurred between 115 and 136 days after insertion. Other studies using different balloon designs reported deflation at around 3–4 months[20,24,25]. In the present series, displacement was seen in 18 instances but only when the IGB had been *in situ* for at least 6 months. Although this newer design of balloon may therefore be more durable, balloon failure still occurs and remains the most common and potentially serious late complication of IGB therapy. In the early part of the study the supplier of the BIB® recommended a 3-month limit for balloon placement but would allow balloons to remain *in situ* for longer if the patient was informed of the potential risks involved. In December 1999 a newer design of balloon was introduced and the manufacturer recommends placement for up to 6 months[26]. During the course of this study the authors have changed practice in the light of experience gained; patients are now seen in the outpatient clinic every 6–8 weeks, plain abdominal radiography is used if indicated to check balloon position, and balloons are removed routinely between 3 and 6 months after placement. No patient in this series suffered peptic ulceration or gastrointestinal bleeding thus illustrating the importance of ulcer prophylaxis with a proton pump inhibitor for the duration of IGB therapy. Patients who failed to attend for outpatient appointments were actively pursued both directly and via the general practitioner. Five patients in this series were completely lost to follow-up. This is of concern but illustrates that the management of this group of patients can be difficult as compliance with treatment is not always optimum. Another confounding factor is that a significant number of patients in this series were referred from outside Merseyside.

The IGB represents a useful temporary device that achieves moderate weight loss in morbid obesity. It is rarely successful alone but is particularly useful for achieving some initial weight loss before a definitive antiobesity procedure, notably LAGB[24]. IGB therapy requires a dedicated antiobesity surgeon working with other members of a multidisciplinary team of endocrinologists, nurses, dieticians and physiotherapists. Strict and regular follow-up together with removal of the device between 3 and 6 months is essential to avoid potentially serious complications.

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Epidemiological study of oesophageal and gastric cancer in south-east England

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Background: This epidemiological study was carried out to establish the magnitude of the changing incidence of gastric and oesophageal cancer.

Methods: Time-trend analyses of subsite-specific cancers of the oesophagus and stomach were performed using data from the Thames Cancer Registry database (1960–1996) for the South Thames Region. The changes in sex ratio and peak age of incidence are reported.

Results: In the upper two-thirds of the oesophagus there was no significant change in the incidence rate, but the lower third of the oesophagus showed a marked rise for both sexes (average annual change +0·05 for men, +0·009 for women). For the gastric cardia, the incidence in males increased (average annual change +0·025), while in females it remained unchanged. Cancers of the oesophagogastric junction showed a clear increase for both sexes (average annual change +0·07 for men, +0·009 for women). There were changes in the sex ratio and peak age of incidence for all subsite cancers for both sexes.

Conclusion: Over a 37-year period the incidence of cancer of the oesophagogastric junction increased threefold, while the incidence of cancers of the other subsites of the stomach decreased. Further studies are needed to investigate the aetiology of these changes.

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Introduction

The rising incidence of cancer of the gastro-oesophageal junction has generated considerable interest. This change was first noted in the late 1980s. Numerous publications from various Western industrialized countries (USA[1], UK[2,3], Iceland[4], Switzerland[5], Norway[6], Denmark[7], Australia[8], New Zealand[9]) have shown a trend which differs from that of the Eastern hemisphere[10,11]. Although the overall incidence of gastric cancers has shown a marked decrease in the West over the past decade[12], recent studies have shown that the changes in incidence over time differ for the different anatomical subsites of the stomach[1–6]. The decline in the incidence seems most pronounced for the distal stomach. However, some studies[1,2,4] have shown an increase in the incidence of adenocarcinoma of the cardia, whereas others[5,6] have failed to confirm this trend. Conflicting data also exist with regard to the incidence of oesophageal cancers[1,2,7,13].

The aim of this study, covering one-tenth of the UK population, was to investigate incidence time trends for cancers of the oesophagus and stomach with special emphasis on the various anatomical subsites and sex differences.

Patients and methods

Cancer registration

The Thames Cancer Registry gathers data on all cancers in the south-east of England. The database for the years 1960–1996 was used to study all the oesophageal and gastric cancers in the South Thames Region (counties of Kent, Sussex, Surrey and boroughs of London south of the River Thames). This region covered a population of 6·4 million in 1960 and 6·7 million in 1996.

The sources of the data are primarily the patients' hospital case notes. Trained Cancer Registry personnel visit hospitals on a monthly basis to gather specific data. Information was obtained from referral letters, endoscopy and operative findings, radiology and histology reports, and the discharge summaries. Therefore, the accuracy of registration depends crucially on the commitment of hospital clinical staff to record correct and complete information, and on the availability of clinical notes. Data were completed with additional information from the Office for National Statistics, death certificates and other cancer registries[14]. Random checks were carried out to ensure that the data recorded in the data sheets corresponded to the correct diagnosis as per patients' notes, in order to eliminate interpretation errors.

Tumour topography

In the Thames Cancer Registry, subsites of the origin of cancers were registered according to the International Classification of Diseases 9th edition (ICD-9) codes[15]. Cancers of the oesophagus were classified as cervical (150.0), thoracic (150.1), abdominal (150.2), upper third (150.3), middle third (150.4), lower third (150.5), overlapping contiguous sites (150.8) and not otherwise specified (150.9). For the purpose of this study, cancers of the oesophagus were analysed in two categories: upper two-thirds (150.0, 150.1, 150.3 and 150.4) and lower one-third (150.2 and 150.5). Categories 150.8 and 150.9 were analysed together as 'oesophagus: part unspecified'.

Cancers of the stomach were classified as those of the cardia (151.0), pylorus (151.1), pyloric antrum (151.2), fundus (151.3), body (151.4), lesser curvature (151.5), greater curvature (151.6), other parts of stomach (151.8) and not otherwise specified (151.9). For the purpose of this study, cancers of the pylorus (151.1) and pyloric antrum (151.2) were analysed together as 'cancers of the distal stomach' (data were available from only 1980 onwards), while the categories 151.8 and 151.9 were analysed as 'stomach: part unspecified'. The other categories were analysed individually.

Statistical analysis

Age-standardized incidence rate per 100 000 world standard population (ASR(W))[14] was used for each subgroup and sex. This is a summary index designed to allow comparison of cancer occurrences between populations that may have different age structures. Point estimates and 95 per cent confidence interval (c.i.) estimates of the average annual change in incidence rates were calculated by fitting a least-squares linear regression model to the incidence rate per 100 000 population[16].

Age and sex ratio analysis

The peak incidences of cancers by age were analysed by classifying the actual number of new cancers seen in the 10-year age groups (i.e. 0–9, 10–19 up to 80 or more years). To eliminate the variation in data due to small numbers of patients, the data for age groups were condensed in 5-year intervals (i.e. 1960–1964, up to 1990–1994, and an average figure per year for each 5-year period was calculated. Thus the mode (maximum frequency) of incidence of cancer was calculated in 10-year age groups. Using this methodology, the trend in peak incidence at particular ages was studied. The sex ratio was calculated as the ratio of the age-standardized incidence rates in the periods 1960–1964 and 1992–1996. Regression analysis by least-squares method of sex ratios per year was carried out for the study period to verify the change in the sex ratio. Point estimates and 95 per cent c.i. were calculated[16].

Results

Validity

Spot checks on the validity and accuracy of the classification of the tumours revealed that these classifications were performed accurately by the Thames Cancer Registry, given the limitation of the recorded information in patients' case notes. This was accomplished by randomly checking patients' case notes from the past 10 years where available (the standard practice of most hospitals is to destroy the case notes 2–5 years after the patient's death) and comparing them with the data recorded in the cancer registry. Data completeness (data capture and data entry) was 99 and 100 per cent for oesophagus and stomach respectively, as reported recently[14].

Oesophageal and gastric cancer

Overall, the incidence of cancer of the oesophagus increased significantly for both sexes (for men, average annual change of + 0·12 (95 per cent c.i. 0·11–0·14) per 100 000 and for women + 0·04 (95 per cent c.i. 0·03–0·05)), while that for stomach decreased significantly (for men, − 0·26 (95 per cent c.i. − 0·29 to − 0·23) and for women −0·16 (95 per cent c.i. − 0·17 to − 0·14)) (*Fig. 1*).

The peak age of incidence for oesophageal cancer for men was the 70–79 years age group throughout this period (1960–1996), while for women it was also the 70–79 years age group (until 1979). After 1980 the peak age of incidence for women shifted to those aged 80 years or more. The sex ratio (M : F) changed from 2 : 1 to 2·4 : 1 (an increase of 0·013 per year; $P < 0{\cdot}01$, 95 per cent c.i. 0·005–0·02)

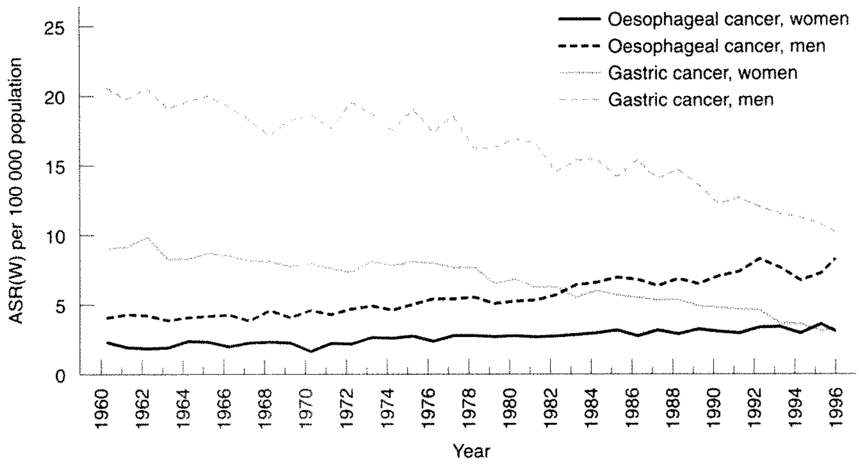

Fig. 1 Oesophageal and gastric cancer in the south-east of England: overall incidence rates. ASR(W), age-standardized incidence rate per 100 000 world standard population

Table 1 Oesophageal cancer

	ASIR*				Sex ratio		
Oesophageal site	1960	1996	Annual change† per 100 000	P	1960	1992	Change
Overall							
Male	4·03 (173)	9·00 (505)	+ 0·120 (+ 0·109, + 0·139)	< 0·001	2·00	2·40	Increase,
Female	2·29 (158)	3·11 (287)	+ 0·041 (+ 0·034, + 0·048)	< 0·001	1	1	$P < 0.01$
Upper two-thirds							
Male	0·59 (26)	1·09 (59)	− 0·003 (− 0·011, + 0·004)	0·40	1·80	1·20	Decrease,
Female	0·30 (19)	0·70 (62)	+ 0·005 (− 0·001, + 0·011)	0·059	1	1	$P < 0.01$
Lower one-third							
Male	0·93 (39)	3·43 (180)	+ 0·048 (+ 0·039, + 0·057)	< 0·001	2·45	3·50	Increase,
Female	0·42 (29)	0·91 (76)	+ 0·009 (+ 0·005, + 0·014)	< 0·001	1	1	$P < 0.01$
'Part unspecified'							
Male	2·51 (108)	4·52 (266)	+ 0·081 (+ 0·064, + 0·098)	< 0·001	1·80	2·30	Increase,
Female	1·57 (110)	1·72 (149)	+ 0·027 (+ 0·018, + 0·036)	< 0·001	1	1	$P < 0.01$

*ASIR, age-standardized incidence rate (world) per 100 000 population; values in parentheses denote the caseload – the number of new cases diagnosed in that year. †Average annual change in ASIR, with 95 per cent confidence intervals in parentheses (least-squares linear regression model)

through the period of this study. The number of new cases of oesophageal cancer diagnosed increased from 173 (1960) to 505 (1996) for men, while for women it increased from 158 to 287 (*Table 1*). Thus the annual number of new cases increased from 331 to 792 in 37 years, a rise of 139 per cent.

The peak age of incidence of gastric cancer in men shifted from the 60–69 years age group (to 1974) to the 70–79 years group. For women the peak incidence moved from the 70–79 years age group (to 1979) to those aged over 80 years. The sex ratio changed from 2·24 : 1 to 3 : 1 (an increase of 0·022 per year; $P < 0.01$, 95 per cent c.i. 0·016–0·027) during this period. The number of new gastric cancers decreased from 886 (1960) to 600 (1996) in men, while in women it decreased from 627 to 342. Thus, the annual number of new cases decreased from 1513 to 942 in 37 years, a fall of 62 per cent.

Subsites for oesophageal cancer

There was no significant change in the incidence rates of cancers of the upper two-thirds of the oesophagus during the period 1960–1996, for both men and women (*Fig. 2*). The peak age of incidence for this subsite in both men and women was the 70–79 years age group throughout the study period of 1960–1996. The sex ratio (M : F) decreased from 1·8 : 1 to 1·2 : 1 (a decrease of 0·021 per year; $P < 0.01$, 95 per cent c.i. −0·03 to −0·009).

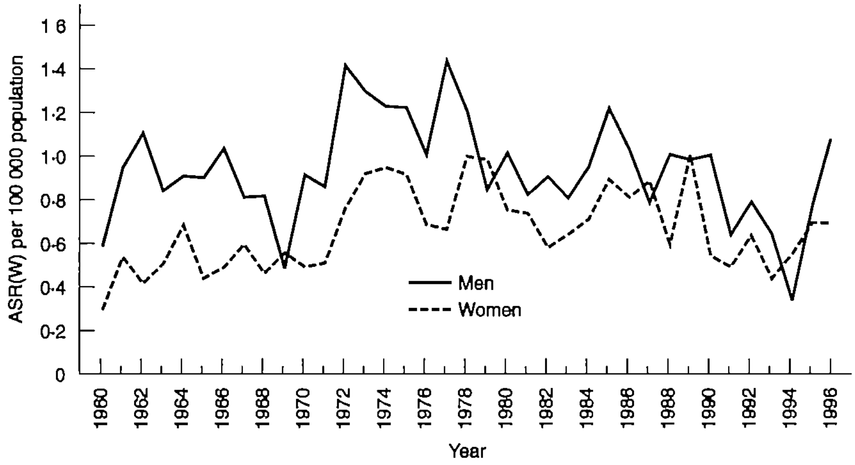

Fig. 2 Incidence rates for cancers of the upper two-thirds of the oesophagus. ASR(W), age-standardized incidence rate per 100 000 world standard population

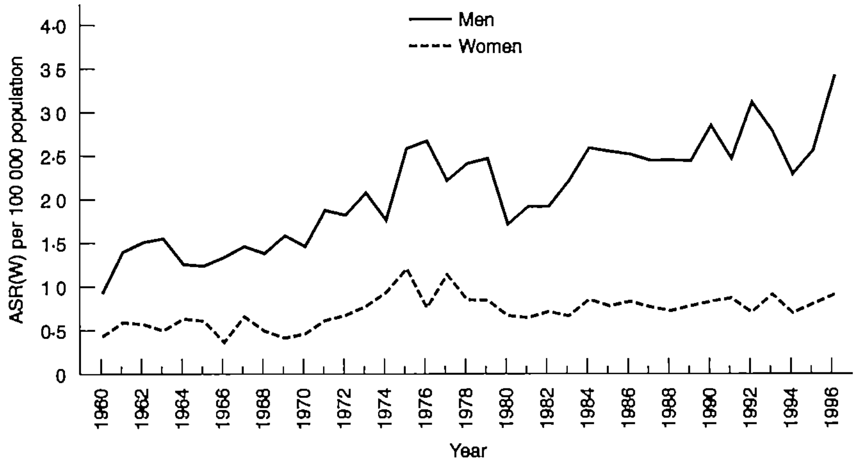

Fig. 3 Incidence rates for cancers of the lower third of the oesophagus. ASR(W), age-standardized incidence rate per 100 000 world standard population

There was a clear increase in the incidence of cancer of the lower third of the oesophagus in men (average annual change +0·05 (95 per cent c.i. 0·04–0·06) per 100 000). There was also an increase in the incidence of lower-third oesophageal cancer in women (+ 0·009 (95 per cent c.i. 0·005–0·014)) (*Fig. 3*). The peak age of incidence for cancers of the lower third for men increased from the 60–69 years age group to the 70–79 years group after 1974. In women it increased from the 70–79 years age group to those aged 80 years or more after 1980. The sex ratio (M : F) rose from 2·45 : 1 to 3·5 : 1 (an increase of 0·027 per year; $P < 0.01$, 95 per cent c.i. 0·01–0·04).

There was a significant increase in the number of cancers classified as 'oesophagus: part unspecified' in both men and women (*Table 1*). Thus, the sex ratio for cancers of the rest of the oesophagus (M : F) rose from 1·8 : 1 to 2·3 : 1 (an increase of 0·018 per year; $P < 0.01$, 95 per cent c.i. 0·006–0·03).

Subsites for gastric cancer

There was a significant increase in the incidence of cancer of the gastric cardia in men over the study period of 1960–1996 (average annual change +0·025 (95 per cent c.i. 0·012–0·037) per 100 000), but not in women ($P = 0.90$) (*Fig. 4*). The rate of increase in men was significant in the period from 1960 to 1979 ($P < 0.01$) and remained constant at the

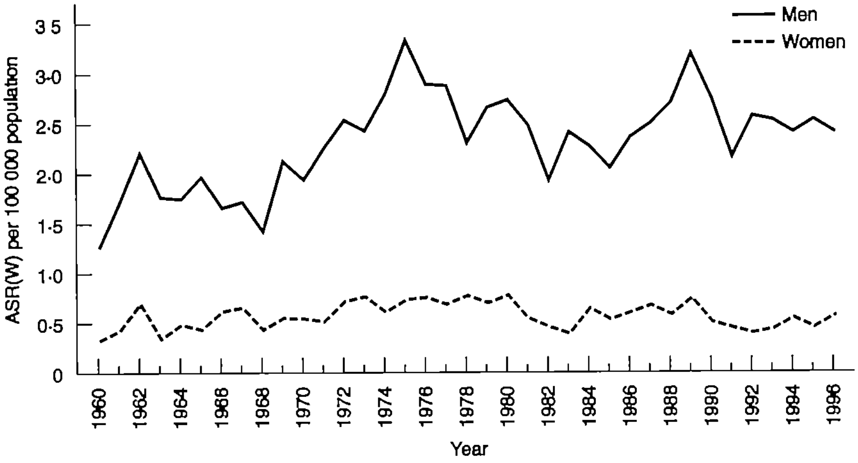

Fig. 4 Incidence rates for cancer of the gastric cardia. ASR(W), age-standardized incidence rate per 100 000 world standard population

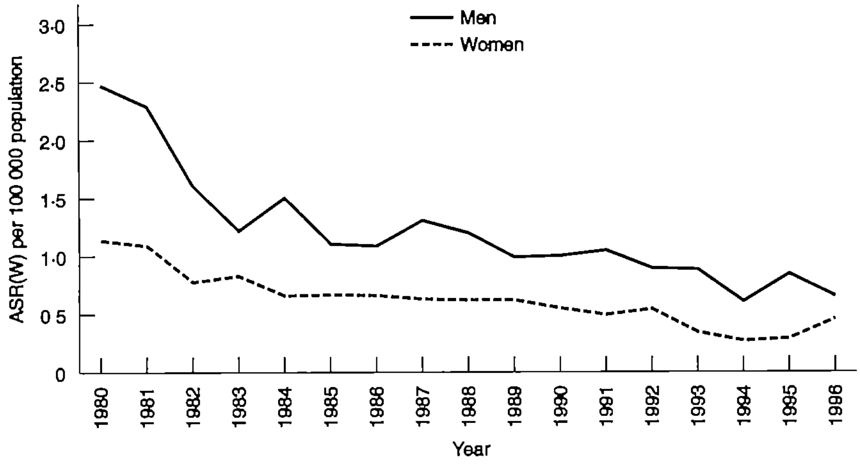

Fig. 5 Incidence rates for cancers of the distal stomach. ASR(W), age-standardized incidence rate per 100 000 world standard population

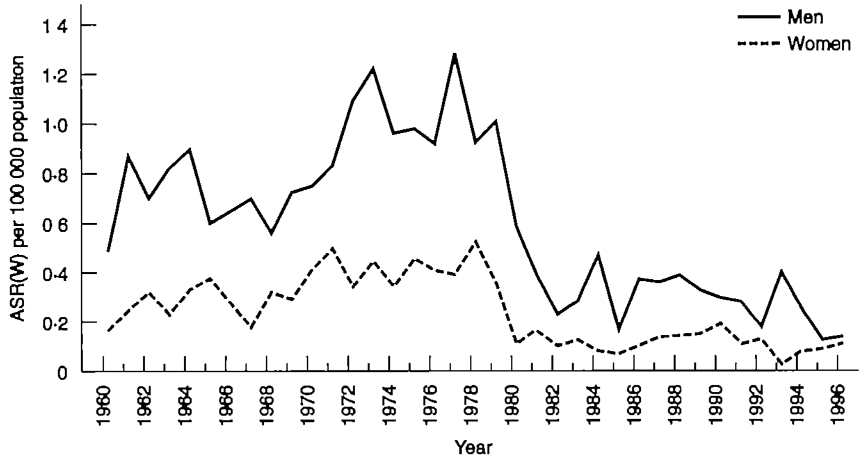

Fig. 6 Incidence rates for cancers of the body of the stomach. ASR(W), age-standardized incidence rate per 100 000 world standard population

Table 2 Gastric cancer

	ASIR*				Sex ratio		
Site in stomach	1960	1996	Annual change† per 100 000	*P*	1960	1992	Change
Overall							
Male	20·65 (886)	10·18 (600)	– 0·262 (– 0·292, –0·232)	< 0·001	2·24	3·00	Increase,
Female	8·99 (627)	3·42 (342)	– 0·157 (– 0·172, –0·141)	< 0·001	1	1	*P* < 0·01
Cardia							
Male	1·24 (53)	2·41 (127)	+ 0·025 (+ 0·012, +0·037)	0·003	3·76	5·30	Increase,
Female	0·33 (23)	0·55 (44)	+ 0·001 (– 0·004, +0·004)	0·902	1	1	*P* < 0·01
Fundus (1961 onwards)							
Male	0·42 (18)	0·15 (10)	– 0·017 (– 0·024, –0·01)	< 0·001	3·50	5·00	No change
Female	0·12 (9)	0·03 (4)	– 0·006 (– 0·008, –0·003)	< 0·001	1	1	
Distal (1980 onwards)							
Male	2·47 (133)	0·63 (37)	– 0·089 (– 0·117, –0·060)	< 0·001	2·17	1·47	No change
Female	1·14 (95)	0·43 (40)	– 0·045 (– 0·055, –0·034)	< 0·001	1	1	*P* = 0·49
Body							
Male	0·49 (21)	0·14 (9)	– 0·019 (– 0·027, –0·012)	< 0·001	3·07	1·27	No change,
Female	0·16 (10)	0·11 (10)	– 0·008 (– 0·011, –0·004)	< 0·001	1	1	*P* = 0·41
Lesser curvature (1961 onwards)							
Male	1·61 (70)	0·45 (28)	– 0·033 (– 0·046, –0·021)	< 0·001	2·63	2·25	No change
Female	0·61 (40)	0·20 (24)	– 0·011 (– 0·016, –0·006)	< 0·001	1	1	
Greater curvature (1961 onwards)							
Male	0·36 (17)	0·15 (8)	– 0·007 (– 0·012, –0·003)	0·002	1·03	1·07	No change
Female	0·35 (19)	0·14 (9)	– 0·002 (– 0·005, +0·001)	0·11	1	1	
'Part unspecified' (1961 onwards)							
Male	14·81 (668)	6·45 (397)	– 0·256 (– 0·284, –0·227)	< 0·001	2·20	2·70	Increase,
Female	7·30 (548)	2·30 (237)	– 0·152 (– 0·163, –0·142)	< 0·001	1	1	*P* < 0·01

*ASIR, age-standardized incidence rate (world) per 100 000 population; values in parentheses denote the caseload – the number of new cases diagnosed in that year. †Average annual change in ASIR, with 95 per cent confidence intervals in parentheses (least-squares linear regression model)

higher level between 1980 and 1996. The sex ratio (M : F) increased from 3·76 : 1 to 5·3 : 1 (an increase of 0·047 per year; $P < 0.01$, 95 per cent c.i. 0·02–0·07). The peak age of incidence in men increased from the 60–69 years age group, to the 70–79 years group after 1979. In women it increased from the 70–79 years age group to the group aged 80 years and over after 1984.

Although the number of cancers seen was small, there was a fall in the incidence of cancer of the gastric fundus in both men (average annual change –0·017 (95 per cent c.i. – 0·024 to – 0·01) per 100 000) and women (average annual change –0·006 (95 per cent c.i. – 0·008 to – 0·003) per 100 000). Cancers of the distal stomach for the period 1980–1996 showed a clear decrease in incidence in both sexes (average annual change per 100 000 was – 0·089 for men, – 0·045 for women) (*Fig. 5*). Overall, there was also a fall in the incidence of cancer of the body of stomach for both sexes (*Fig. 6*), but in the period from 1960 to 1979 there was a significant increase for both sexes ($P < 0.01$). Between 1980 and 1996 the incidence rate was constant at a low level. The incidence of cancer of the lesser curvature decreased in both sexes (average annual change per 100 000 was – 0·033 for men, – 0·011 for women), and for cancer of the greater curvature there was a significant decrease for men (average annual change per 100 000 was – 0·007) but there was no change for women. Cancers classified as 'stomach: part unspecified' reduced significantly in incidence (*Table 2*). The sex ratio (M : F) for cancers of the rest of the stomach changed from 2·2 : 1 to 2·7 : 1 (an increase of 0·018 per year; $P < 0.01$, 95 per cent c.i. 0·01–0·02).

Cancer of the oesophagogastric junction (*Fig. 7*)

For this analysis, cancers of the lower one-third of the oesophagus and those of the gastric cardia were combined and analysed as one entity. These cancers showed a marked increase in both sexes (average annual change per 100 000 was + 0·072 (95 per cent c.i. 0·054–0·090) for men and

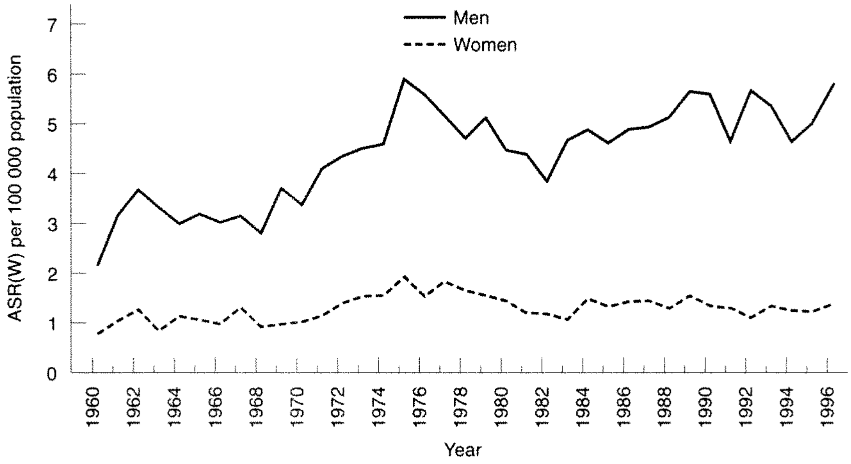

Fig. 7 Incidence rates for cancers of the oesophagogastric junction. ASR(W), age-standardized incidence rate per 100 000 world standard population

+ 0·009 (95 per cent c.i. 0·002–0·017) for women). The sex ratio (M : F) also increased markedly, from 3 : 1 to 4·2 : 1, in the last 5 years of the study.

Discussion

This analysis of the Thames Cancer Registry data showed divergent trends for the various subsites of oesophageal and gastric cancer in both sexes, during the period 1960–1996.

Overall, there was a highly significant increase in the incidence of oesophageal cancer and a decrease in gastric cancer for both sexes within the period studied, thus confirming the findings of previous studies[4,6,7,12,13]. While most subsites showed a preponderance to the male sex, cancers of the upper two-thirds of the oesophagus showed an increased predilection for the female sex; the sex ratio of cancers of the body, curvatures and distal part of the stomach has remained unchanged. Furthermore, the peak incidence of age for these cancers and their subsites changed over this time period. These epidemiological changes may be important in identifying possible causative factors for these cancers.

Most studies have grouped cancers of the oesophagogastric junction (i.e. cancers of the lower third of the oesophagus and gastric cardia) as a single entity[2,17,18]. Interestingly, in this study, cancers of the lower third of the oesophagus and those of the gastric cardia exhibited different epidemiological features, suggesting that these may be aetiologically different. When analysed together as cancers of the oesophagogastric junction, cancers of the lower third of the oesophagus were greatly in the majority, and therefore dominated the summative analysis. This suggests that these cancers may be different in their pathogenesis. Similar results have been observed by others[6]. Of course, it is possible for clinicians to misclassify cancers of these subsites, leading to an apparent increase in the cancers of one or the other subsite[19]. However, discordant trends were noted in the two sexes and this explanation is unlikely to be the only cause of the rise in the incidence of gastric cardia cancer in men.

The incidence of cancers of the body, lesser curvature and greater curvature of the stomach showed a decreasing trend in both sexes, although this was most marked in the distal stomach. Interestingly, the incident sex ratio showed a marked increase in the upper stomach, while for the other subsites it was constant. This suggests that cancers of the proximal stomach are changing differently from those of the distal stomach in both incidence and sex ratios.

The role of good data and data analysis is the formation of a sound knowledge base, which will help to formulate healthcare policies, from which, ultimately, survival improvements may be seen[20]. The data rely heavily on clinicians' records in the hospital notes. Unfortunately, these were sometimes incomplete or imprecise. In some cases, the exact site of the cancer may not have been recorded by the attending physician. This explains the relatively high number of entries in the 'not otherwise specified' (150.9 and 151.9) and 'other parts' (150.8 and 151.8) subheadings. However, the only cancers used for data analysis of various subsites in the present study were those that were specifically labelled so. Furthermore, it does appear that the trend of the 'part unspecified' cancer parallels that of the organ as a whole in all aspects. For subsites, however, the trend may be in opposing directions. Therefore, it would not be unreasonable to assume that the distribution of cancers in the 'part unspecified' group is similar that of the organ as a whole.

To establish the histological certainty of diagnosis, other studies have relied on data from resected specimens only[3,4]. Unfortunately, this excludes all patients who have not had resectional surgery and thus these studies may not represent true epidemiological trends. Previous studies based on cancer registry data have assumed that histologically unverified data are equally distributed among the histological types of adenocarcinoma and squamous cell carcinoma[2,6]. This assumption may be inaccurate, as the sex ratios and the peak age of incidence were shown to have changed in the time period studied. Also, in records where histologically verified data were available there was a change in the ratios of oesophageal squamous cell carcinomas and adenocarcinomas[2].

Various hypotheses have been postulated for the causes of the changing epidemiological trends. The most widely acceptable hypothesis is that of the increasing incidence of gastro-oesophageal reflux[21]. A population-based case–control study suggested a strong relationship between gastro-oesophageal reflux and oesophageal adenocarcinoma (and a weaker relationship with gastric cardia cancer)[22]. Conflicting evidence exists regarding the role of acid suppressants in the pathogenesis of oesphagogastric junction cancer[23,24]. A reduction in the rate of infection with *Helicobacter pylori* in Western countries over the past few decades could account for the decrease in incidence of distal gastric cancers[25–27]. Furthermore, an inverse relationship between upper gastric cancer and *H. pylori* infection has been suggested[28]. The roles of alcohol and tobacco[29–33] and of dietary and racial differences[34–36] have been studied, but thus far evidence is conflicting. The exact aetiology of the major changes in the epidemiology of gastric and oesophageal cancer remains unclear.

The most worrying finding of this study was confirmation of the relatively rapid rise in the incidence of oesphagogastric cancers. The rate of rise of this tumour is currently unmatched by any other tumour in the Western world. Cancers of the lower third of oesophagus and the gastric cardia exhibited different epidemiological traits in this study. Better documentation of the exact subsite for gastric and oesophageal cancers by clinicians is required (possibly exact subsite coding by the treating clinician). This would help epidemiological trends to be elucidated with more confidence. The evidence available regarding pathogenesis is currently not strong enough to enable clinicians to advise on cancer prevention, and therefore further increases seem inevitable. Currently, the best management is early detection of the disease. Public awareness of cardinal symptoms needs to be increased and systems to ensure early diagnosis need to be strengthened, in line with recently published guidelines[37].

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Original article

Glove powder promotes adhesion formation and facilitates tumour cell adhesion and growth

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Background: The presence of foreign material in the abdominal cavity irritates the peritoneal surface, leading to an inflammatory response. This defensive mechanism can provoke adhesion formation. The same peritoneal defence cascade is thought to play a role in the process of intra-abdominal tumour recurrence. The aim of this study was to evaluate whether glove powder produced peritoneal adhesions in a rat adhesion model and whether it promoted intra-abdominal tumour recurrence in a rat tumour cell adhesion and growth model.

Methods: A reproducible model that allowed semiquantitative scoring of adhesion formation or tumour load was used in three different groups of rats. One group was treated by intra-abdominal application of powder obtained from starch-powdered gloves, one by application of pure starch and in one group no powder was used.

Results: Application of glove powder or pure starch on minimally and severely traumatized peritoneum gave rise to significantly greater adhesion formation and intra-abdominal tumour load than peritoneal trauma alone (both $P < 0{\cdot}001$).

Conclusion: Starch-induced peritoneal trauma leads not only to more adhesion formation but also to increased adhesion and growth of tumour cells. Since good powder-free alternatives are available there is no longer any justification for the use of powdered gloves during intra-abdominal surgery.

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Introduction

Postoperative adhesions are abnormal unions between peritoneal surfaces that occur after almost every intra-abdominal surgical intervention and can lead to a number of complications. A variety of therapeutic modalities to reduce postoperative adhesion formation has been studied but clinically useful therapy is not currently available. The sole available strategy to reduce postoperative adhesions is prevention by limiting peroperative trauma of the peritoneum. Several studies have shown that exposure of peritoneum to starch powder present on surgical gloves leads to an inflammatory response of the peritoneum and contributes to adhesion formation[1–6]. Exposure of already injured peritoneal surfaces to starch enhances the intensity of the peritoneal reaction and gives rise to more and stronger adhesions than peritoneal trauma or starch alone[7,8].

In previous animal studies, the authors have shown that surgical trauma of the peritoneum promotes adhesion formation and that the intensity of the inflicted trauma correlates with the extent of adhesion formation[9]. One aim of the present study was to evaluate whether the observed effect of glove powder on peritoneal adhesion formation could be reproduced in a rat adhesion model and to differentiate whether starch powder alone or other glove contents are responsible for peritoneal damage and subsequent adhesions.

Following potentially curative resection of gastrointestinal carcinoma, local recurrence and peritoneal dissemination are common sites of tumour recurrence[10]. Distribution patterns of first peritoneal recurrence show that the resection site is preferential, and combined recurrence on peritoneal surfaces and resection site is common[11]. Early preoperative tumour cell seeding and peroperative shedding of tumour cells, due to handling the tumour and leakage from dissected lymphatic channels, are the most likely causes of tumour recurrence[11]. The tumour cell entrapment theory proposes that the fibrinous exudate, formed as an initial response to surgical trauma of the peritoneum, facilitates implantation of cancer cells[11]. The dynamic cascade of peritoneal healing, induced by peritoneal damage, leading to adhesion formation also seems to be important in the process of intraperitoneal adhesion and growth of tumour cells. Indeed, previously described clinical and experimental studies have shown that surgical trauma may promote intra-abdominal tumour recurrence[12–14]. The degree of inflicted peritoneal trauma correlates with the extent of intra-abdominal tumour load[14].

The secondary aim of this study was therefore to analyse whether the traumatic effect of glove powder on peritoneum also promotes intra-abdominal tumour recurrence.

Materials and methods

Animals

Female inbred WAG rats of reproductive age weighing 120–160 g were obtained from Harlan, Austerlitz, The Netherlands. They were bred under specific pathogen-free conditions, kept under standard laboratory conditions (temperature 20–24°C, relative humidity 50–60 per cent, 12-h light and 12-h dark cycles) and fed with standard rat food and water *ad libitum*. The experimental protocol adhered to rules laid down by the Dutch Animal Experimentation Act and was approved by the Committee on Animal Research of Erasmus University Rotterdam, The Netherlands.

Surgical gloves and isolation of glove powder

Starch-powdered gloves (Baxter, Utrecht, The Netherlands) were cut into pieces of 1 × 1 cm. The glove parts were washed in phosphate-buffered saline by gentle stirring for 24 h. Subsequently the suspension was filtered over a stericup filter with a pore size of 0·22 μm (Millipore, Ettenleur, The Netherlands). The particles left behind on the filter (glove-covering starch powder and other small glove contents) were centrifuged (2500 r.p.m. for 10 min). The supernatant was removed and the pellets were left to dry under sterile conditions for 24 h. The powder obtained was used for further experiments.

Pure starch

To investigate whether starch alone or in combination with other glove contents was responsible for any effects on adhesion formation and tumour cell adhesion and growth, all experiments were also performed using pure starch (Regent Hospital Products, London, UK). Some 3 mg glove powder or pure starch was used in subsequent experiments. This dose is large compared with the amount of glove powder that might be left in the peritoneal cavity during laparotomy in humans. However, laparotomy in humans lasts longer than laparotomy in rats, so glove powder may irritate the peritoneum for a longer period.

Tumour

Tumour CC531 is a moderately differentiated, weakly immunogenic, colonic adenocarcinoma induced in WAG rats by 1,2-dimethylhydrazine[15]. It is transplantable in syngeneic WAG rats. The tumour is maintained as a cell culture in RPMI 1640 medium supplemented with 5 per cent foetal calf serum (screened for viruses and *Mycoplasma*), 1 per cent penicillin (5000 units/ml), 1 per cent streptomycin (5000 units/ml) and 1 per cent L-glutamine (200 mmol/l). Medium and all supplements were obtained from Life Technologicals, Breda, The Netherlands. Cells were passaged once a week using 0·05 per cent trypsin and 0·02 per cent ethylenediamine tetra-acetic acid. Before use *in vivo*, tumour cells were harvested from stationary cultures by gentle trypsinization (5 min at 37°C), centrifugation (5 min at 700*g*) and resuspension in RPMI 1640, providing cell suspensions with a viability greater than 95 per cent. CC531 is relatively insensitive to chemotherapy but sensitive to the effects of biological response modifiers.

Operative procedures

To study the effect of glove powder and pure starch on adhesion formation and tumour recurrence in rats, previously described, reproducible, rat adhesion and tumour adhesion and growth models were used[9,14]. Briefly, under ether anaesthesia and aseptic conditions a laparotomy was performed using a lower midline incision of 5 cm. Three Surgilene® 5/0 sutures (Braun, Melsungen, Germany) were applied to both lateral peritoneal sides 0·7 cm apart and 1·5 cm away from the abdominal incision. All knots were double, fastened tightly to ensure local ischaemia. Both uterine horns were exposed, not handled, and sutured to the lateral peritoneum with Surgilene® 6/0 proximally and distally from the three 5/0 sutures. In this way a standardized amount of minimal peritoneal trauma was inflicted. Standardized severe peritoneal trauma was inflicted by additively rubbing the exposed uterine horns with surgical Medipres® gauze (van Heek Medical, Losser, The Netherlands) before suturing to the lateral abdominal wall. Rubbing was performed with a device that enabled application of a constant pressure of 120 g/cm^2. The uterine horns were rubbed ten times over their total length.

Minimally and severely traumatized peritoneal sides were treated locally by application of 3 mg powder obtained from the starch-powdered gloves, by application of 3 mg pure starch, or were not exposed. The abdomen was closed

Table 1 Tumour scoring system based on the peritoneal cancer index[17]

Score	Characteristics
0	No tumour growth
1	Estimated tumour diameter of less than 0·5 cm
2	Estimated tumour diameter between 0·5 and 1 cm
3	Estimated tumour diameter between 1 and 2 cm
4	Estimated tumour diameter between 2 and 3 cm
5	Estimated tumour diameter of more than 3 cm

in two layers with 5/0 polyglycolic acid and 2/0 silk sutures (Braun).

Experimental design

In 20 rats standardized minimal peritoneal trauma was inflicted to both lateral peritoneal sides. In ten rats glove powder was applied on one uterine horn while the other uterine horn was not exposed. In the other ten rats pure starch was applied on one uterine horn while the other was not exposed.

In 19 rats standardized severe peritoneal trauma was inflicted to both lateral peritoneal sides. In nine rats glove powder and in ten rats pure starch was applied on one uterine horn, while in both groups the other uterine horn was not exposed to powder or starch.

A further nine rats underwent an operation during which both uterine horns were exposed and sutured to the lateral peritoneum. No powder was applied. Before closing the abdomen, $0{\cdot}5 \times 10^6$ CC531 tumour cells, in 1 ml RPMI 1640, were injected intraperitoneally, 0·5 ml along the left and 0·5 ml along the right abdominal wall. Another nine rats underwent the same operative procedure with the additional application of 3 mg glove powder on each uterine horn. Nine rats underwent the same procedure during which 3 mg pure starch was applied on both uterine horns.

Evaluation of adhesion formation

Some 14 days after laparotomy the rats were killed for assessment of intra-abdominal adhesion formation. Macroscopically the adhesions were scored according to extent (quantity) and type (quality) by two independent observers. The extent of adhesion formation was quantified by dividing the area to be scored into eight by means of the three 5/0 sutures in the lateral peritoneum. The presence or absence of adhesions in the eight demarcated areas was scored. Adhesions in an area accounted for 12·5 per cent of adhesions; thus a maximum of 100 per cent adhesions could be scored. In each rat two lateral peritoneal sides were assessed. The types of adhesions formed were classified macroscopically using the Zühlke classification[16].

Evaluation of intraperitoneal tumour cell adhesion and growth

Some 21 days after operation all rats were killed and intraperitoneal tumour load was scored semiquantitatively at the following peritoneal sites: right uterine horn, left uterine horn, subcutaneously (at the site of the operative scar), parietal peritoneum (at the lateral abdominal wall sides where no uterine horns were fixated), kidney, liver, retroperitoneum and omentum. The scoring was performed by two independent observers and ranged from 0 to 5 per site (*Table 1*). For each rat the score at peritoneal sites, except for the uterine horns, was added, from which a mean total tumour load per rat could be estimated. In the present study the term tumour recurrence was used to illustrate tumour load, which is the net result of tumour cell adhesion and tumour growth, because it is presumed that intraperitoneal injection of tumour cells resembles the clinical situation of tumour cell spill during tumour resection.

Statistical analysis

The mean(s.d.) percentage adhesion was calculated per group. Statistical analysis was performed with a *t* test for paired samples and an unpaired Student's *t* test as appropriate.

The median (range) intraperitoneal tumour load at each scored abdominal site and total tumour load were calculated per group. Statistical analysis was performed with the Kruskal–Wallis test to determine overall differences, followed by the Mann–Whitney *U* test to compare differences between groups. $P < 0{\cdot}05$ was considered statistically significant.

Results

None of the rats was found to have adhesions at the initial operation. There were no postoperative complications such as bowel obstruction, peritonitis or tumour overgrowth.

Adhesion formation

Table 2 shows that application of glove powder, after minimal peritoneal trauma, led to significantly more adhesion formation than minimal peritoneal trauma alone ($P < 0{\cdot}001$). Local application of pure starch also induced a significantly higher mean percentage adhesion than

Table 2 Adhesions and Zühlke score after minimal peritoneal trauma alone or combined with application of glove powder or pure starch

	*n**	Adhesion formation† (%)	Zühlke score
No powder	10	33(10)	1–2
Glove powder	10	84(13)	2–3‡
No starch	10	35(10)	1–2
Pure starch	10	81(9)	2–3‡

*Number of peritoneal sides (uterine horns) assessed. †Values are mean(s.d.). ‡$P < 0{\cdot}001$ *versus* no powder or starch (paired *t* test)

Table 3 Adhesions and Zühlke score after severe peritoneal trauma alone or combined with application of glove powder or pure starch

	*n**	Adhesion formation† (%)	Zühlke score
No powder	10	72(10)	2–3
Glove powder	10	97(6)	3‡
No starch	10	71(10)	2
Pure starch	10	96(6)	3‡

*Number of peritoneal sides (uterine horns) assessed. †Values are mean(s.d.). ‡$P < 0{\cdot}001$ *versus* no powder or starch (paired *t* test)

minimal peritoneal trauma alone ($P < 0{\cdot}001$). The mean percentage adhesion found in the glove powder group did not differ significantly from that of the pure starch group. Adhesions formed after minimal peritoneal trauma were filmy (Zühlke type 1–2), involving only pelvic fat. Adhesions found after local application of glove powder or pure starch were stronger (Zühlke type 2–3) and involved pelvic fat, uterine horn and small bowel.

Table 3 shows that local application of powder obtained from starch-powdered gloves or pure starch induced additional adhesion formation, even in the presence of severe trauma to the peritoneal surface. Both gave rise to a significantly higher mean percentage adhesion than severe peritoneal trauma alone ($P < 0{\cdot}001$). As in the previous experiment, there was no significant difference in the adhesion-inducing capacity of glove powder and pure starch. Adhesions found after Medipres® rubbing of the uterus horn were dense and thick (Zühlke type 2–3), whereas application of glove powder or pure starch on severely traumatized peritoneum led to even stronger adhesions (Zühlke type 3).

Intraperitoneal tumour cell adhesion and growth

Table 4 summarizes results observed at peritoneal sites where glove powder or pure starch was applied (uterine horns) in comparison with controls. Glove powder as well as pure starch evoked a significant increase in tumour load at the uterine horns ($P < 0{\cdot}001$). Application of glove powder or pure starch gave rise to similar results.

The median total peritoneal tumour load in rats treated with glove powder or pure starch, measured at peritoneal sites other than the uterine horns, differed significantly from the median total peritoneal tumour load in controls (*Table 5*) ($P = 0{\cdot}002$ and $P = 0{\cdot}001$ respectively). These differences were due mainly to differences at the site of the scar and omentum. Again, treatment with glove powder or pure starch did not induce a significantly different extent of total tumour load.

Table 4 Tumour load at uterine horns fixed only to the lateral peritoneum, and treated with glove powder or pure starch after fixation

	n	Tumour load*
No powder	9	0 (0–1)
Glove powder	9	4 (3–5)†
Pure starch	9	4 (3–5)†

*Values are median (range). †$P < 0{\cdot}001$ *versus* no powder (Kruskal–Wallis test with Mann–Whitney *U post hoc* test)

Table 5 Tumour load at different peritoneal sites in rats having laparotomy followed by fixation of the uterine horn alone or combined with application of glove powder or pure starch

Abdominal site	No powder (*n* = 9)	Glove powder (*n* = 9)	Pure starch (*n* = 9)
Subcutaneous	1 (0–1)**	1 (1–4)*	1 (1–3)
Parietal peritoneum	1 (0–1)†	1 (0–2)	1 (0–2)
Kidney	1 (0–2)	1 (1–2)	1 (0–2)
Liver	0 (0–2)	1 (0–2)	1 (0–2)
Retroperitoneum	1 (0–3)	1 (1–2)	1 (1–3)
Omentum	1 (0–2)†	2 (1–4)‡	2 (1–3)
Total	1 (0–2)§	1 (1–2)¶	1 (1–2)

Values are median (range). *$P = 0{\cdot}006$, ‡$P = 0{\cdot}04$, ¶$P = 0{\cdot}002$ *versus* no powder; **$P = 0{\cdot}006$, †$P = 0{\cdot}04$, §$P = 0{\cdot}001$ *versus* pure starch (Kruskal–Wallis test with Mann–Whitney *U post hoc* test)

Discussion

Since the introduction of surgical gloves in 1896, several components and additives have been used in the glove industry to facilitate manufacturing and to lessen the hazards associated with glove use[4]. Modern gloves are made of two main components: rubber and glove lubricants. Glove lubricants have been associated with a number of iatrogenic problems in surgical patients[4]. In particular, starch powder in surgical gloves can lead to serious complications such as granulomatous peritonitis and adhesion formation and potentiation of infection[18], which may in turn give rise to serious complications such as intestinal obstruction, infertility and chronic pelvic pain. The exact pathogenic mechanism(s) behind the undesirable reactions to starch granules is not clear and may be diverse[19]. A possible (host defence) cascade by which starch increases the propensity of tissues to form adhesions starts with irritation of the peritoneum by starch particles, which leads to reduced fibrinolysis and activation of neutrophils and macrophages[20,21]. Activated macrophages produce oxygen free radicals, prostaglandin E_2, thromboxane B_2 and various cytokines that are part of the fibrotic process[21]. The authors have previously shown that the degree of peritoneal trauma correlates with the extent of adhesion formation[9]. In the present experiments, using the same model, powder obtained from starch-powdered gloves as well as pure starch significantly increased adhesion formation. There was no difference in the capacity to induce adhesions between glove powder and pure starch. These results support the hypothesis that starch is the main component of powdered gloves that promotes adhesion formation as a result of a direct effect on the peritoneum.

The authors have previously suggested that the peritoneal defence mechanism triggered by surgical trauma to the peritoneum not only promotes adhesion formation but also stimulates tumour recurrence[14]. Several theories relate to the underlying mechanisms of the adhesion and growth of spilled tumour cells. According to the theory of metastatic efficiency, implantation of tumour cells on to raw tissue surfaces is a more efficient process than implantation on intact surfaces[11]. The fibrin entrapment hypothesis proposes that tumour cells are trapped in fibrin at the resection site and abraded peritoneal surfaces, thereby providing protection from host defence mechanisms[22]. In peritoneal wound healing, inflammatory and mesothelial cells produce an abundance of cytokines and growth factors, which might also be beneficial for tumour cell adhesion and tumour growth[23–25]. Indeed, a significant correlation between the intensity of surgical trauma to the peritoneum and the degree of tumour recurrence can be demonstrated in a rat tumour adhesion and growth model[14]. In the present study, using the same experimental model, the traumatic effect of glove powder and pure starch promoted adhesion and growth of free intra-abdominal tumour cells. The most impressive tumour load was found at directly traumatized peritoneal sites (sites to which glove powder or starch was applied). However, the tumour cell adhesion and growth-promoting effects of glove powder and starch were not confined to the traumatized peritoneal sites, as tumour load was also significantly higher at remote sites.

Despite the evidence in support of starch-induced complications, a considerable number of general surgeons continue to wear starch-powdered gloves[26]. It has been shown that careful washing of powdered gloves with saline fails to remove all the starch and even results in clumping of the residual starch granules[7]. Cleansing with povidone–iodine and sterile water does reduce the amount of starch particles[27], but povidone–iodine itself induces adhesion formation[28]. The present study shows that starch-induced peritoneal trauma leads not only to adhesion formation but also to adhesion and growth of free intra-abdominal tumour cells. As good powder-free alternatives are available, there is no longer any justification for the use of powdered gloves during intra-abdominal surgery.

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Rectal adenocarcinoma with liver metastases: management of the primary tumour (*Br J Surg* 2001; 88: 163–4)

Sir

We disagree that the prophylactic resection of the primary tumour is associated with a mortality rate of 15 per cent. Our experience and data from the literature show mortality rates of around 5 per cent for patients with stage IV disease[1,2].

We question the authors' advice to avoid prophylactic resection in patients with unresectable distant disease. Most of these patients had H1 disease[2] (less than 25 per cent parenchymal replacement) and were potential candidates for liver-directed therapies such as cryoablation and, more recently, radiofrequency ablation. A study of 123 patients with unresectable hepatic malignancies treated with radiofrequency ablation showed no mortality, low morbidity and, at a median follow-up of 15 months, a 1·8 per cent recurrence rate at the site of radiofrequency ablation and 27·6 per cent new metastatic disease[3]. A trial combining radiofrequency ablation with hepatic artery infusion chemotherapy via an implantable pump was initiated in an attempt to reduce recurrence rates and enhance long-term survival.

Decision on the management of the primary tumour in patients with unresectable liver metastases must always take account of the potential of ablative therapies before definitive answers can be obtained from clinical trials.

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Authors' reply

Sir

Our operative mortality statistics were derived from the most recent population-based audit of colorectal cancer management in the UK[1] where the operative mortality rate for patients with Dukes' stage D disease was 15·9 per cent. For scheduled/elective operations the mortality rate was 8 per cent, which is substantially higher than that of 3–5 per cent for patients with Dukes' stages A, B or C disease.

With regard to unresectable liver metastases we agree that alternative treatment modalities such as radiofrequency ablation show promise but we consider systemic chemotherapy to be the standard treatment[2]. We take an aggressive approach to resection of liver metastases in preference to other modalities, and have found that the majority of patients with unresectable disease have more extensive liver disease than reported by Scoggins *et al.*[3]. In our series of 24 patients in whom the primary tumour was managed nonoperatively, only one patient with metastases replacing less than 25 per cent liver parenchyma, and no extrahepatic disease, was deemed unresectable. It is surprising that 68 per cent had less than 25 per cent involvement but the factors determining unresectability of liver metastases in those patients are not stated[3].

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Single-blind randomized clinical trial of laparoscopic *versus* open appendicectomy in children (*Br J Surg* 2001; 88: 510–14)

Sir

This prospective study comparing laparoscopic with open appendicectomy in children recruited patients with clinical features of uncomplicated acute appendicitis. To exclude from the final analysis 12 patients (16 per cent) with the operative finding of either localized or generalized peritonitis, some of whom in the laparoscopic group may have been converted to an open procedure, will inevitably skew the results in favour of laparoscopic surgery. An indication of the number of converted laparoscopic procedures would have been helpful and an analysis of the data on an intention-to-treat basis would have provided a more realistic evaluation of the role of laparoscopic appendicectomy in children. The only time in the early postoperative period in which there was a significant difference in the requirement for rescue analgesia was within the first 4 h, suggesting that intraoperative analgesia was inadequate. Wound infiltration with bupivacaine has been shown to reduce both postoperative analgesic requirements[1] and hospital stay[2] in children undergoing appendicectomy. Its use in the current study may have reduced the need for rescue analgesia in both groups and negated the small difference in analgesic requirements between the two surgical approaches. Finally, while statistically significant, the economic value of a mean hospital stay of 0·7 days is questionable and the conclusion that laparoscopic appendicectomy resulted in an overall reduction in hospital costs is not supported by the presentation of any health economic data.

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Authors' reply

Sir

We agree that surgery for acute appendicitis differs from that for appendicitis with localized or generalized peritonitis. We have just finished analysing the outcome of children with complicated appendicitis or extra-appendiceal pathology and hope to submit this manuscript to the journal shortly. We agree that good pain treatment is essential for every child undergoing surgery and have published extensively in this field over the past 9 years. We agree that different local anaesthetic techniques play an important role in postoperative pain management in children and should be used more widely.

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Variation in clinical decision making is a partial explanation for geographical variation in lower extremity amputation rates (*Br J Surg* 2001; 88: 529–33)

Sir

The authors successfully demonstrate individual variation in clinical decision making in lower extremity amputations and this may be relevant for other surgical procedures as well. I believe it would have been relevant to categorize the surgeons involved on the basis of years of vascular experience and annual workload[1]. Disparity in results of revascularization is well known. The 3-year secondary patency rates for distal bypass vary from 41 to 69 per cent[2,3]. Age, experience of the surgeon and personal results may be crucial points in clinical decision making. The younger consultant's enthusiasm to perform a distal microvascular bypass to smaller pedal vessels may not be matched by a senior surgeon trying to give the patient a better quality of life by amputation based on personal experience. Trying to establish guidelines based on logistic regression models may make treatment options uniform but may not achieve the desired effect of providing a better quality of life.

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Author's reply

Sir

The question of whether both the number of years of vascular surgery experience held and the annual workload influence the decisions made by vascular surgeons regarding revascularization or amputation of a lower limb is important but difficult to answer. Our sample of ten vascular surgeons had all been consultants for at least 5 years and while one of the centres did have less throughput (as indicated by theatre time available and number of clinics held) the small number of surgeons in our study make any *post hoc* analysis unreliable.

The general issue of volume and outcome from hospital care was the subject of an 'Effective Health Care' review[1]. With regard to amputation of the lower limb the review included only the study by Flood *et al.*[2], which showed that patients treated in low volume American hospitals had a standardized mortality ratio for lower limb amputation of 1·11 compared with 0·94 in high volume hospitals ($P < 0.05$). Even here, however, the direction of causality, the selection bias of accessibility and the residual confounding by case-mix complicate any firm conclusions being drawn and this study certainly does not provide evidence that experience and volume are determining factors for outcome (or the decision to pursue one or other treatment). This is therefore an area where we must conclude the case 'not proven'.

On the second point we agree with Mr Saklani. The production of guidelines based on logistic regression cannot be uncritically accepted as 'best practice'. Further studies on the quality of life experienced by patients undergoing both revascularization and amputation will be necessary to refine any future consensus approach to guideline construction.

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Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer (*Br J Surg* 2001; 88: 400–4)

Sir

We were surprised at the conclusion of this work that a primary defunctioning stoma did not reduce the complications of anastomotic leakage. The recommendation that larger studies are required to investigate the long-term results can surely no longer be justified. This observation is further supported by the paper by Edwards *et al.*[1] in the same issue who confirm multiple earlier reports that, while diversion of the faecal stream following colorectal or coloanal anastomoses probably does not reduce the incidence of leaks, it will reduce the complications[2–4]. The possibility of mortality from a leak, the significant morbidity and the fact that even in the study, one-third of patients with leakage required a permanent stoma, surely represents an unacceptable risk[5].

The paper also concludes that the 'functional results in patients who had a defunctioning stoma closed were inferior to those experienced by patients without an anastomotic leakage'. This is somewhat confusing. Were the patients included in this group primarily defunctioned or was the stoma the result of the re-operation? Surely this will have further influence on the outcome of function.

In reality does this paper not simply reiterate the argument that patients undergoing total mesorectal excision should indeed be defunctioned?

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Authors' reply

Sir

The routine use of a protective stoma in patients undergoing total mesorectal excision with low anastomosis is still debated. The policy of defunctioning should be based on the answers to the following questions. Does the routine use of a defunctioning stoma reduce the incidence of leaks? Does it influence the early complication rate and late anorectal function following a leak? No randomized studies comparing patients with and without a primary defunctioning stoma using current methods of intestinal reconstruction have been published. Our study did not intend to give answers to these questions but to compare the late anorectal function in a group of patients who had experienced anastomotic leakage – irrespective of primary defunctioning – to that of control patients who had not. The first group did indeed have impaired long-term function.

We were surprised to observe that the early and long-term consequences of anastomotic leakage were similar in the five patients who were defunctioned primarily and the 12 patients who were not. As no randomization had been performed and the number of patients was small, no conclusions can be drawn with regard to these questions. We maintain that larger studies are necessary to clarify whether primary defunctioning will affect the long-term consequences of leakage.

We now routinely use a protective stoma in patients who have a low anastomosis. The rationale for this is not yet evidence-based, but we believe that the incidence of leakage may be somewhat lower, and the early consequences of a leak less dramatic. Larger, randomized studies evaluating the influence of primary defunctioning on the incidence and consequences of leakage from colonic J-pouch anastomoses would be interesting.

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Randomized clinical trial of local bupivacaine perfusion *versus* parenteral morphine infusion for pain relief after laparotomy (*Br J Surg* 2001; 88: 357–9)

Letter 1

Sir

I wonder if the authors could provide a reference or data to support the statement 'although opioids remain the mainstay for decreasing postoperative pain…', as in my experience the use of patient-controlled analgesia (PCA) for postoperative pain control is at least equalled, if not exceeded, by the use of epidural anaesthesia.

Significance is attached to the difference in the median total amount of morphine used between the two groups under comparison. That there should be a difference seems to be a statement of the obvious – one group is being treated with a morphine PCA and the other is not. I fail to see the clinical significance of this observation.

The incision crosses two or possibly three dermatomes. Would epidural anaesthesia not be the analgesia of choice in such a situation (none of the patients entered into the trial appeared to have a contraindication based upon the information provided)?

I would disagree with the conclusion that 'This technique is a feasible and safe alternative to patient-controlled morphine analgesia', in view of the 300 per cent increase in the wound infection rate in the infusion group. Though not statistically significant, one wonders if this trend would be significant if a larger number of patients had been studied.

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Letter 2

Sir

We agree that local infusion of bupivacaine is a safe and effective alternative to parenteral opiates but are not convinced that this study supports this conclusion. It is common practice, if epidural blockade is not used, to infiltrate the wound with local anaesthetic to provide early postoperative pain relief, regardless of the subsequent mode of analgesia. This was not performed in the opiate group and therefore may account for the only difference in pain scores between the two groups – the lower pain scores on day 1 in the bupivacaine group. Additionally the clinical significance of the statistically significant difference in opiate use between one group being given morphine as the primary form of analgesia and one group where it is used as a rescue analgesia is not made clear in the text.

Physiological and psychological interpatient variability in analgesia requirement means that patients require different amounts of opiate or bupivacaine to provide pain relief. Studying rescue analgesia once adequate analgesia is achieved 6 h postoperatively would allow for these variables and would provide a useful comparison of efficacy and safety between these groups.

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Author's reply

Sir

If epidural blockade is as effective as suggested, then why the need for early postoperative pain relief with local wound anaesthetic? We were using patient-controlled anaesthesia and not epidural blockade.

Our study showed that high doses of morphine are not necessary after laparotomy. There was no difference in pain scores between the two groups except for lower pain scores on day 1 in the bupivacaine group. This shows that intravenous morphine is not needed routinely and this is emphasized by the relatively small number of patients needing rescue morphine in the bupivacaine group.

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Review of current practice to establish success after vasectomy (*Br J Surg* 2001; 88: 290–3)

Sir

We agree with the suggestion that the strict requirement of two consecutive azoospermic postvasectomy semen specimens may be unjustified, leads to a high level of non-compliance and causes unnecessary delay in confirming success of the procedure. Our current practice is to carry out one postvasectomy semen analysis after 30 postvasectomy ejaculations. Only if spermatozoa are sill present do we repeat this after 50 postvasectomy ejaculations. It is probably the number of postvasectomy ejaculations that is the most important factor in clearance of residual sperm from the ampulla of the vas deferens. We have found a higher compliance using this method, with 100 per cent of patients returning adequate postvasectomy azoospermic specimens. Ninety-eight per cent of patients (457 of 462) obtained this result at 30 postvasectomy ejaculations and 100 per cent by 50 postvasectomy ejaculations. To date there have been no failures following this regimen.

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Author's reply

Sir

We agree that the timing of postvasectomy specimens is not the critical factor in clearance of the spermatozoa from the genitourinary tract but the number of postvasectomy ejaculations. In our routine postoperative instruction to patients following vasectomy we explain that regular ejaculation is important and recommend a minimum of 20 ejaculations prior to specimen examination which, for convenience, is timed at 4 months.

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Revisiting transtibial amputation with the long posterior flap (*Br J Surg* 2001; 88: 683–6)

Sir

This review omits the report by Ruckley *et al.*[1] of a multicentre trial of the skew flap technique. Robinson[2] also showed that this technique had significant advantages when compared with other available methods. The skew flap technique makes logical use of the blood supply in most patients. The scar is remote from the bone ends and the soft tissue is pre-formed to the ideal shape for the patellar tendon-bearing prostheses. Walking aids can be used early and a socket made without delay, and these factors help borderline patients to retain mobility.

Our experience in a rehabilitation unit is that some problems are encountered with the long posterior flap procedure. The distal stump is bulky and the healing of the anterior scar is liable to breakdown. This may lead to delay in walking and the fitting of a patellar tendon-bearing socket. The anterior scar may subsequently break down at the kick point inside the socket.

The claim that the long posterior flap procedure cannot be bettered is not supported. The procedure that is likely to give the best result in the individual patient should be selected.

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1 Ruckley CV, Stonebridge PA, Prescott RJ. Skewflap *versus* long posterior flap in below-knee amputations: multicenter trial. *J Vasc Surg* 1991; **13**: 423–7.
2 Robinson KP. Skew-flap below-knee amputation. *Ann R Coll Surg Engl* 1991, **73**: 155–7.

Authors' reply

Sir

We apologize for our oversight in omitting these papers from our bibliography but neither paper demonstrates that the skew flap is better than the long posterior flap.

In Mr Robinson's own paper (reference two) the frequency of secondary surgery was 18 of 131 which is not significantly different to our own rate of 67 of 395. Our patients typically begin mobilization on a temporary prosthesis at 5 days and are cast at 21 days. The figure of 95 per cent rehabilitation to independent walking is very impressive but we need to know the transfemoral to transtibial ratio during the period of the study to put the figures in context. We addressed the problem of a bulky stump by complete excision of the soleus.

Ruckley *et al.* (reference one) demonstrated by randomized controlled trial that there was no difference in early healing and no significant difference in terms of final outcome at 6 months. Their methodology did not allow them to assess the speed of rehabilitation and they do not state the time interval to limb fitting for either group even though the patients stayed on the surgical ward for an average of 36 days for skew flap and 42 days for long posterior flap.

We therefore stand by our original conclusions.

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Surgery

J. D. Corson, R. C. N. Williamson (eds)

297 × 254 mm. Pp. 1660. Illustrated. 2001. London: Mosby. £130·00.

This is the heaviest general surgical textbook I have encountered (15 lbs) – are its contents metaphorically as heavy? In my opinion it is the result of remarkable cooperation between over 250 authors, most of whom are from either side of the Atlantic pond; all the authors have been appropriately chosen to provide comprehensive and up-to-date chapters on their specific interests. The differences in practice are clearly lessening between the USA and Europe, even though American English prevails. The volume is a treasure-trove of outstanding clinical photographs, radiographs and superb colour diagrams, all specifically and uniformly put together for the book. Teachers will be pleasantly surprised to find all this excellent material also presented on a CD ROM, which will be useful for personal and tutorial work – the restrictions for use are made clear. There is a slightly quirky page reference system, as the book is in seven sections, but this is soon comprehensible. All the chapters appear to reflect current opinion based on reviewed evidence and there are large reference lists, approximately up to 1998, following each chapter. This work will appeal to surgical trainees who will find it useful for the scientific basis of surgery on their way to consultant clinical practice. It will also be useful for those studying for Board and Intercollegiate examinations, to whom I strongly recommend it. The large sections on practical problems will be particularly attractive in this respect, as will be the final section on allied surgical specialties. My only reservation is the book's size; it will not travel well and may have been better in two volumes with a more rigid spine. Congratulations go to the two main editors for achieving a readable consistent style throughout.

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Surgical Laparoscopy. 2nd Ed.

K. A. Zucker (ed)

285 × 219 mm. Pp. 844. Illustrated. 2000. Philadelphia:
Lippincott Williams & Wilkins. $225·00.

This is the second edition of a 10-year-old book which contains 70 chapters by 100 contributors who are mostly from North America. It aims to be a comprehensive minimal access surgery text and, as a result, has many redundant chapters for the average laparoscopic specialist. However, as might be expected in a multi-author book, there are some excellent chapters and some rather indifferent ones; there is nothing for the urologist. The editor has deliberately tried not to interfere with the individual style of the authors which, while leading to some repetition, has also ensured more information about different techniques. The title is misleading in that there are chapters on thoracoscopy, head and neck surgery, lower limb venous disease and transanal endoscopic microsurgery. There are (unexpectedly) chapters on the medical management and preoperative evaluation of gastro-oesophageal reflux disease. There is a large and very good section on the fundamentals of laparoscopic surgery. The best chapters are those on electrosurgery and ultrasonography, fundoplication, common bile duct exploration, acute cholecystectomy and medical malpractice in laparoscopic surgery. The chapter on thoracoscopic splanchnicectomy was disappointing. Overall, the advantages of this publication outweigh the disadvantages and I recommend it as a good all-round general text containing some excellent operative descriptions.

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Endovascular Grafting: Advanced Treatment for Vascular Disease

M. L. Marin, L. H. Hollier (eds)

260 × 183 mm. Pp. 192. Illustrated. 2000. Armonk: Futura. $85·00.

This monograph is the first of a series with an entirely American authorship who are mainly from the Mount Sinai Medical Centre, New York. There are short chapters on all aspects of endovascular grafting for both aneurysmal and occlusive vascular disease. Although the format has been carefully edited to ensure consistency, the text is repetitive. For instance, Parodi's 1991 publication features in almost every chapter introduction. Many of the chapters give results of individual clinical series, and there is a comprehensive account of the repair of peripheral artery aneurysms using endovascular techniques, with the delivery devices discussed in detail. However, the chapter describing classification of endoleaks does not give adequate practical information on how to manage the condition. While the references are modern, with the most recent in 1999, a book such as this that describes rapidly evolving techniques is inevitably out of date before it is published. It is directed at the specialist who may be about to commence an endovascular programme and, while it gives an overview of the results and techniques involved, it does not provide adequate detail to commission and run an endovascular unit. Access to internet databases renders publications such as this obsolete.

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Principles and Practice of Renal Transplantation

B. D. Kahan, C. Ponticelli

250 × 193 mm Pp. 846 Illustrated 2000 London Martin Dunitz £149 95

This is undoubtedly the best book on renal transplantation that I have seen in the past 25 years. It is written by two masters in the field, who on some chapters collaborate with other experts. The initial chapters cover the basic science of transplantation, dealing with histocompatibility and the immunobiology of rejection. The next few chapters deal with recipient and donor selection, the transplant operation and its surgical complications. Other text deals with immunosuppressive agents, particularly their mechanisms of action, clinical effects and pharmacokinetics, and the remainder of the book is devoted to rejection, recurrence of primary disease, medical complications, psychiatric problems, and obstetric and gynaecological considerations, with a final chapter on the results of transplantation. There is a worthwhile section on the use of computerization for efficient information management, analysis of data and strategic decision making. The book is beautifully produced on good quality paper. All the chapters are clearly written with up-to-date references. Particularly helpful is the liberal use of tables, bullet points and figures, which draw attention to the main points in the text. The colour illustrations and radiography are of extremely high quality; the photomicrographs in the chapter on rejection and recurrent primary disease are beautifully reproduced in colour and extremely clear.

There is something in this book for everybody involved in renal transplantation from the immunobiologist to the trainee in renal transplantation and histopathology. The topics are well selected and clearly presented and I can thoroughly recommend this book to everybody involved in renal transplantation.

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Pancreatic Tumors: Achievements and Perspectives

C. G. Dervenis, C. Bassi (eds)

238 × 170 mm Pp. 409 Illustrated 2000 Stuttgart Georg Thieme €126·80

The 3rd International Meeting on Pancreatic Diseases held in Athens in May 1999 is now presented in book format. The objective was to 'design a complete work on the subject which would prove useful to all colleagues interested in the field'. Internationally renowned experts have, in 47 chapters, discussed pancreatic tumours from an introductory chapter on the history of resection of the pancreas, via molecular biology to treatment, concluding with four chapters on 'future perspectives'. There is variation in the quality of the chapters, from less than two pages with limited information and an incomplete reference list to extensive narrative reviews with more than 200 references. The thematic overlap between chapters and inconsistency in format could have been eliminated. Some of the chapters would have benefited from linguistic revision. I was interested in those on an international documentation system (which we need) and those relating to quality of life issues (which is so important in this disease) but they contained limited guidance. The foreword states that this book is 'founded on the bedrock of evidence based medicine'. I agree that the book is rich in information, but readers must decide for themselves whether the book adds knowledge.

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Scientific Surgery

The *BJS* is committed to the practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English-language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on the *BJS* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

CoStasis Multi-centre Collaborative Writing Committee. A novel collagen-based composite offers effective haemostasis for multiple surgical indications: Results of a randomized controlled trial. *Surgery* 2001; **129**: 445–50.

The study involved 347 patients having general, cardiac, hepatic and orthopaedic surgery. Bleeding was controlled within 10 min in 90 per cent of patients treated with the collagen haemostat compared with 58 per cent of controls ($P = 0{\cdot}01$).

Long KH, Bannon MP, Zietlow SP, Helgeson ER, Harmsen WS, Smith CD *et al.* A prospective randomized comparison of laparoscopic with open appendectomy: clinical and economic analyses. *Surgery* 2001; **129**: 390–400.

Some 198 patients were included. Laparoscopic surgery took longer, was less painful, reduced hospital stay (2·6 *versus* 3·4 days, $P < 0{\cdot}01$) and speeded return to normal activity. Hospital costs were similar.

Moore M, Burak WE Jr, Nelson E, Kearney T, Simmons R, Mayers L *et al.* Fibrin sealant reduces the duration and amount of fluid drainage after axillary dissection: a randomized prospective clinical trial. *J Am Coll Surg 2001*; **192**: 591–9.

In this multicentre study, fibrin sealant reduced the amount of drainage from the axillary wound ($P < 0{\cdot}05$) and also from the mastectomy wound ($P = 0{\cdot}01$).

Baguneid MS, Welch M, Bukhari M, Fulford PE, Howe M, Bigley G *et al.* A randomized study to evaluate the effect of a perioperative infusion of dopexamine on colonic mucosal ischemia after aortic surgery. *J Vasc Surg* 2001; **33**: 758–63.

Thirty patients all had colonoscopy and biopsy 1 week after surgery. Dopexamine seemed to protect the colonic mucosa as significantly fewer patients had histological evidence of ischaemia after 1 week (8 *versus* 1, $P = 0{\cdot}05$).

Porrett TRC, Lunniss PJ. A prospective randomized trial of consultant-led injection sclerotherapy compared with nurse practitioner-led non-invasive interventions in the management of patients with first and second degree haemorrhoids. *Colorectal Disease* 2001; **3**: 227–31.

Nurse-led education, advice and bowel habit training was as effective as sclerotherapy in improving symptoms from bleeding haemorrhoids after 6 months in this study of 25 patients.

Pitt J, Dawson PM, Hallan RI, Boulos PB. A double-blind randomized placebo-controlled trial of oral indoramin to treat chronic anal fissure. *Colorectal Disease* 2001; **3**: 165–8.

Indoramin (20 mg b.d.) reduced anal resting pressure by 30 per cent but was ineffective in healing chronic anal fissures (after 3 months: 1 of 14 *versus* 2 of 9 placebo) in this study including 25 patients.

Udelsman R, Westra WH, Donovan PI, Sohn TA, Cameron JL. Randomized prospective evaluation of frozen-section analysis for follicular neoplasms of the thyroid. *Ann Surg* 2001; **233**: 716–22.

Sixty-one operations were included. Frozen section analysis made the definitive diagnosis of malignancy in one of 29 patients; six others were later found to have a carcinoma. Three of 31 patients in the control group had cancer on definitive histology. There were no clinical differences in the outcomes.

Armstrong DN, Ambroze WL, Schertzer ME, Orangio GR. Harmonic scalpel *versus* electrocautery haemorrhoidectomy: a prospective evaluation. *Dis Colon Rectum* 2001; **44**: 558–64.

Fifty patients with grade 3 piles were studied. Both pain and requirement for analgesia were significantly less up to 28 days after surgery with the harmonic scalpel. One week after operation 55 per cent of the harmonic scalpel patients were at work compared to 23 per cent after electrocautery.

Stewart HJ, Prescott RJ, Forrest PM. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. *J Natl Cancer Institute* 2001; **93**: 456–62.

This update reported median follow-up of 15 years in 1323 patients. The beneficial effects of tamoxifen on total survival, relapse rate and death from breast cancer were preserved to 15 years, but there was no advantage found for continuing tamoxifen for more than 5 years after surgery.

Meier DE, Nkor SK, Aasa D, OlaOlorun DA, Tarpley JL. Prospective randomized comparison of two preoperative skin preparation techniques in a developing world country. *World J Surg* 2001; **25**: 441–443.

Some 200 patients having inguinal hernia repair were randomized to a cheap, locally available soap and spirit skin preparation or a more expensive imported povidone iodine solution. Infection rates were similar (5·1 *versus* 5·9 per cent respectively).

Durkin MT, Turton EPL, Wijesinghe LD, Scott DJA, Berridge DC. Long saphenous vein stripping and quality of life – a randomized trial. *Eur J Vasc Endovasc Surg* 2001; **21**: 454–9.

Some 87 patients were randomized to perforate invagination or conventional stripping with quality of life analysis after 6 weeks and 6 months. Both groups had improved quality of life after 6 months but it was better in several domains after perforate invagination stripping.

The *BJS* website can be found at *http://www.bjs.co.uk*. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

British Association of Endocrine Surgeons Abstracts

The following abstracts were presented at the British Association of Endocrine Surgeons meeting held in Plymouth, UK on 25 May 2001.

The *BJS* prize was awarded to the presentation: 'Who performs thyroid surgery – a review of current otolaryngological practice' by J. D. Ramsden, A. P. Johnson, H. C. Cocks and J. C. Watkinson.

Non-invasive imaging of insulinomas and gastrinomas with endoscopic ultrasonography and somatostatin receptor scintigraphy

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Background: The aim was to evaluate the results of two non-invasive imaging studies for preoperative localization of insulinomas and gastrinomas.

Methods: This was a retrospective study of 54 patients with histologically proven insulinomas (29 patients) or gastrinomas (26 patients) who underwent operation from March 1991 to March 2000. One patient had both types of tumour. The results of endoscopic ultrasonography (EUS; $n=47$) and somatostatin receptor scintigraphy (SMS; $n=42$) were correlated with intraoperative findings, pathological results and outcome of the secretory syndrome.

Results: Sensitivity and positive predictive value (PPV) of EUS were 80 per cent (24 of 30) and 92 per cent (24 of 26) respectively for intrapancreatic insulinomas and gastrinomas, 46 per cent (six of 13) and 100 per cent (six of six) for duodenal gastrinomas, and 65 per cent (11 of 17) and 73 per cent (11 of 15) for metastatic nodes. Sensitivity and PPV of SMS were 47 per cent (eight of 17) and 89 per cent (eight of nine) for insulinomas. For gastrinomas, sensitivity and PPV were 20 per cent (one of five) and 100 per cent (one of one) respectively for pancreatic gastrinomas, 65 per cent (15 of 23) and 100 per cent (15 of 15) for duodenal tumours and periduodenal nodes, and 71 per cent (five of seven) and 71 per cent (five of seven) for hepatic metastases. Sensitivity of EUS and SMS combined was 94 per cent (15 of 16) for insulinomas and 94 per cent (17 of 18) for gastrinomas. Only one patient operated on for an insulinoma was not cured; it was malignant. Sixteen of 26 patients operated on for gastrinoma were cured. In two of the latter, preoperative imaging was negative, and in two others it showed only part of the tumour. Therefore in four of 16 patients whose gastrinoma was cured, surgical exploration was critical for cure.

Conclusion: EUS and SMS should be considered as the initial preoperative imaging procedures for insulinomas and gastrinomas, and render more invasive procedures unnecessary for most patients. The sensitivity of SMS for insulinomas and of EUS for duodenal gastrinomas remains moderate and renders surgical exploration of the whole duodenopancreas mandatory.

Laparoscopic adrenalectomy and the indications for adrenal surgery

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Background: Laparoscopic adrenalectomy (LA) is now considered the gold standard for adrenal surgery. Its low invasiveness could theoretically widen the indications for a surgical approach to adrenal lesions. The aim of this study was to evaluate how the introduction of LA changed the profile of patients referred for surgery.

Methods: Two hundred and forty-three patients underwent adrenal surgery between November 1986 and December 1999. They were divided into two groups according to the period in which they were operated: patients in group 1 underwent surgery before the introduction of LA (November 1986 to May 1993) and those in group 2 underwent operation after the introduction of LA (June 1993 to December 1999). The two periods were of 79 months. The two groups were compared for gender, age, preoperative diagnosis and lesion size.

Results: Group 1 included 88 patients (36·2 per cent) and there were 155 (63·8 per cent) in group 2. The rate of adrenal operations was 1·11 per month during the first period and 1·96 per month during the second. No statistically significant differences were found between the two groups with respect to gender and lesion size. Statistical analysis showed significant differences in age ($P=0{\cdot}04$) and preoperative diagnosis ($P=0{\cdot}005$), in particular for the percentage of patients with incidentaloma (35·5 per cent in group 2 *versus* 21·6 per cent in group 1) and metastases (7·7 per cent in group 2 and none in group 1).

Conclusion: The introduction of LA resulted in a sharp increase in the number of patients referred. The mean size of the lesions removed did not differ significantly, showing that dimensional criteria for patient selection did not change. The presence of older patients in group 2 could be justified by the more favourable postoperative outcome of LA. The improvement in imaging techniques and the advantages of LA in terms of postoperative course might explain the higher percentage of incidentalomas and metastases among the patients in group 2.

Doxazosin *versus* phenoxybenzamine in the perioperative management of α-adrenoceptor blockade in patients with phaeochromocytoma

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Background: Despite adverse side-effects phenoxybenzamine has been widely used in the preoperative management of patients with phaeochromocytoma. Doxazosin, a specific α_1-adrenoceptor antagonist, has a pharmacological profile more suited to control of blood pressure in such patients.

Methods: A sequential study of 26 patients with phaeochromocytoma encompassed a definite and prescribed change in preoperative drug management from phenoxybenzamine to doxazosin. Haemodynamic, pharmacological and biochemical indicators of α- and β-adrenoceptor blockade were measured before, during and after anaesthesia and surgery in eight patients pretreated with phenoxybenzamine, and 18 patients pretreated with doxazosin.

Results: Doxazosin was as effective as phenoxybenzamine in controlling arterial pressure and heart rate before and during surgery, but caused fewer undesirable side-effects, both before and after operation. Following phenoxybenzamine therapy substantial α_1-adrenoceptor blockade persisted for more than 2 days after operation, whereas after doxazosin it was undetectable on the first postoperative day.

Conclusion: Doxazosin 2–8 mg day^{-1} provided safe and efficacious preoperative and perioperative control of arterial pressure. In patients with predominantly noradrenaline-secreting tumours, the pretreatment 24-h urinary noradrenaline excretion gave an indication of the daily doxazosin requirement.

Outcome of non-operated adrenal masses

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Background: Computed tomography performed for non-adrenal-related symptoms detects an adrenal mass or 'incidentaloma' in 0·4–4·3 per cent of patients. Most authors advocate a non-operative policy after minimal careful investigations aimed at excluding phaeochromocytoma and aldosteronoma. The breakthrough of laparoscopic adrenalectomy has led some to challenge this approach. This retrospective study focuses on the outcome of patients with non-operated adrenal masses.

Methods: From 1986 to 1999, 126 patients (64 men) presented with an incidental mass of the adrenal fossa, and a non-surgical approach was followed. Mean size was 36·5 mm diameter. All patients underwent in-depth clinical, biochemical and imaging investigations, and were stratified into two groups: group 1, no contraindication to surgery ($n = 95$); and group 2, contraindication to surgery (frail patients, invasive adrenal or metastatic extra-adrenal cancer) ($n = 31$).

Results: At a mean follow-up of 4·3 years, 17 patients (13·5 per cent) were lost to follow-up, including 11 of 95 in group 1. There were 36 deaths (28·5 per cent) including 12 of 95 in group 1 (no adrenal-related death) and 24 of 31 in group 2. Seventy-two patients were alive and well without operation, including only one in group 2. A benign adrenal adenoma was removed from one patient at the time of surgery for aortic aneurysm. Eight adrenal masses disappeared spontaneously, eight moderately increased in size and none underwent malignant degeneration.

Conclusion: Careful clinical and biochemical investigations, imaging and nor-iodocholesterol scintigraphy with definite uptake by the adrenal mass are strong indicators of benign disease and allow a conservative approach.

Weiss scoring revisited

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Background: The 'gold standard' for the diagnosis of malignant adrenocortical tumours is the presence of distant metastasis or local recurrence. Weiss scoring is one of the best available histopathological methods for discerning malignancy. This scoring may help determine which patients require chemotherapy but interpretation of the nine Weiss criteria is sometimes difficult or subjective. The aim of this study was to evaluate Weiss scoring by retrospective study of 50 adrenocortical tumours and to specify some of the criteria. Concurrently, the value of an immunohistochemical stain for M1B1 (a marker of proliferation) was assessed.

Methods: Twenty-five adrenocortical tumours with metastasis or recurrence were paired, based on functional status, with 25 adrenocortical tumours without metastasis or recurrence. Mean clinical follow-up was 60·9 months. These 50 tumours were analysed with Weiss scoring. Each of the nine criteria was defined precisely. Immunohistochemical staining using fixed, paraffin-embedded sections was performed. The percentage of cells showing M1B1 nuclear immunoreactivity was assessed.

Results: The presence of three or more of the nine Weiss criteria was related to clinical malignancy (sensitivity 100 per cent, specificity 96 per cent). Each of the nine criteria was significantly correlated to malignancy ($P < 0·01$). Only one tumour with three of the nine criteria had a benign course during a 4-year clinical follow-up. The percentage of cells staining positively for M1B1 was significantly higher in malignant tumours than in those with a benign course ($P < 0·01$). Large tumours (more than 62 g or 7·25 cm) had a high probability for malignancy (sensitivity 96 and 96 per cent, specificity 96 and 96 per cent, respectively).

Conclusion: This retrospective study confirms the value of Weiss scoring for establishing malignancy in adrenocortical tumours. Tumours exhibiting three Weiss criteria are rare and should still be considered to be of undetermined prognosis. Moreover, the results indicate that M1B1 immunostaining is helpful in the distinction between benign and malignant adrenocortical tumours.

First-time operation for primary hyperparathyroidism: is the BAES standard defendable?

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Background: The British Association of Endocrine Surgeons (BAES) has set a standard that no less than 95 per cent of patients undergoing surgery for primary hyperparathyroidism (HPT) should be normocalcaemic at the end of the first operation. The arrival of a new consultant provided an opportunity to investigate the outcome of patients undergoing first surgical exploration for HPT in this institution.

Methods: A prospective audit was undertaken of the outcome of 100 consecutive patients undergoing a first exploration for HPT. Reasons for failed explorations were examined.

Results: Between November 1996 and May 2000, 100 patients (84 female, 16 male) underwent bilateral neck exploration for HPT. Median age was 60 (range 12–88) years. Median preoperative calcium concentration was 2·89 (range 2·60–4·46) mmol l^{-1} and the parathyroid hormone level was 110 (range 41–1400) pmol l^{-1}. Commonest symptoms at referral were bone and/or joint pain (55 per cent), depression (27 per cent) and renal colic (19 per cent). Pathologies included adenoma (90 per cent), hyperplasia (4 per cent), double adenoma (3 per cent) and carcinoma (2 per cent). Ten glands were ectopic (nine intrathymic, one undescended). After first exploration 94 per cent of patients were normocalcaemic. After second exploration ($n = 5$) 98 per cent were normocalcaemic and after third exploration ($n = 1$) 99 per cent were normocalcaemic. Median weight of the adenoma was 700 (range 130–14 800) mg. Twenty-nine adenomas weighed less than 450 mg. Of the failed explorations ($n = 6$), five glands were intrathymic; the site of the sixth gland remains unknown as the patient refused further investigation. Reasons for failure included missing a second (thymic) adenoma ($n = 2$) and misinterpretation by surgeon ($n = 4$) and pathologist ($n = 3$) of sequestered thyroid tissue. No patient died and the morbidity rate was 8 per cent.

Conclusion: A success rate of 94 per cent after a first operation and 99 per cent after reoperative surgery is compatible with published series, yet fails to satisfy the BAES standard. Improved rapport with the pathologist, more surgical experience and preoperative localization to identify ectopic adenomas may result in greater success. However, the high prevalence of smaller tumours might hinder progress. A standard set too high is demoralizing and paves the way for a hostile medicolegal environment.

National survey of surgical management of primary hyperparathyroidism

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Background: During the past decade the surgical management of primary hyperparathyroidism has been limited to patients with symptoms or complications of the disease. Two recent leading articles, however, have supported the role of early surgical intervention in these patients. The aim of this study was to define the current surgical management of primary hyperparathyroidism in the UK and Ireland.

Methods: A postal questionnaire was sent to all members of the British Association of Endocrine Surgeons in November 2000. The surgeons were asked about their current criteria for patient selection, methods of preoperative localization and operative technique.

Results: Questionnaires were returned from 67 (73 per cent) of 92 surgeons currently performing parathyroid surgery in the UK and Ireland. The mean age of the surgeon was 50·3 (range 37–63) years. The mean number of parathyroidectomies performed per annum was 23·1 (range 0–120), the majority of patients being either asymptomatic (12 per cent) or minimally symptomatic (52 per cent). There was marked variability among surgeons in the use of preoperative localization; sestamibi was used by 39 per cent and ultrasonography by 39 per cent, while 39 per cent of surgeons used no imaging at all. Access to the parathyroids was via a collar incision in 97 per cent and the midline in 96 per cent. Intraoperative localization was aided by routine frozen-section analysis in 73 per cent and use of a neoprobe in 4 per cent. Intraoperative parathyroid hormone was measured by 9 per cent of surgeons. The commonest method of skin closure was subcuticular suture (58 per cent); drains were used either always (36 per cent) or selectively (47 per cent). The mean inpatient stay was 2·6 days.

Conclusion: The results of this survey demonstrate marked variability in the method(s) of preoperative localization. If more patients with this disease are to be referred for surgery more research is required to identify the most cost-effective way of managing these patients.

Patients with a raised serum level of parathyroid hormone after parathyroidectomy show signs of decreased peripheral parathyroid hormone sensitivity

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Background: Concern has been raised regarding increased levels of parathyroid hormone (PTH) in normocalcaemic patients after surgery for parathyroid adenoma. These patients have normal parathyroid and renal function but show signs of remineralization of cortical bone, decreased calcium absorption and low levels of vitamin D. The authors have hypothesized that a decreased peripheral PTH sensitivity could be of importance.

Methods: Thirteen patients operated on for a solitary parathyroid adenoma with a mean(s.d.) preoperative calcium level of 2·72(0·12) mmol l^{-1} were included in the study. All patients had normal renal function and were normocalcaemic after operation. Six weeks after surgery, patients with normal ($n = 5$) and raised ($n = 8$) serum levels of PTH were investigated with a standardized PTH (1–34) infusion test for 6 h.

Results: Patients with a raised level of PTH had a smaller increase in the serum level of ionized calcium during the infusion test (mean(s.d.) 0·02(0·03) mmol l^{-1}) than patients with normal PTH levels (0·06(0·02) mmol l^{-1}) ($P < 0{\cdot}05$). Patients with a raised PTH level also showed a smaller decrease in the serum levels of phosphate ($P < 0{\cdot}05$) and a larger decrease in the excretion of urinary calcium ($P < 0{\cdot}05$). The increase in 1,25 dihydroxyvitamin D did not differ between the two groups of patients.

Conclusion: The present investigation demonstrates that patients operated on for parathyroid adenoma with a raised postoperative serum level of PTH have a decreased calcaemic response to infused PTH. It is hypothesized that these patients have a decreased peripheral sensitivity to PTH, possibly because of long-standing hyperparathyroid disease.

Quality of life after minimally invasive *versus* open parathyroidectomy

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Background: Quality of life improves significantly after successful parathyroid surgery and normalization of serum calcium levels. What is not known is how much of that effect is related to the patient's perception of the procedure, and whether or not patients may perceive that a minimally invasive operation provides a better outcome, and thus a better postoperative quality of life, than an open procedure. The hypothesis was tested that the surgical approach influences perception of outcome. It was expected that patients undergoing minimally invasive parathyroidectomy would report a better quality of life after operation than those undergoing open parathyroidectomy.

Methods: Some 200 consecutive patients who had undergone parathyroid surgery were selected for telephone interview. One hundred and fifty had had an open parathyroidectomy and 50 a minimally invasive procedure, either endoscopically assisted or by a direct minimal access approach. Postoperative quality of life was assessed both with a generic instrument, the Short Form-36 Health Survey (SF-36) and a disease-specific questionnaire. The SF-36 results were compared with those in a matched Australian population.

Results: Patients who underwent direct minimal access parathyroidectomy had significantly better vitality and emotional role limitation scores than those having an open procedure, but there were no differences when all patients who had a minimally invasive procedure (minimal access and endoscopically assisted procedures) were compared with those having an open procedure. The health status scores of all patients having surgery for primary hyperparathyroidism were significantly lower in five of the eight domains than those of a matched Australian population. There was a significantly lower incidence of postoperative symptoms in the minimally invasive group as a whole compared with the open group, and a significantly greater proportion of patients returned to normal daily duties earlier than those who had an open procedure.

Conclusion: Minimally invasive parathyroidectomy is associated with a greater improvement in postoperative quality of life despite the fact that both result in equivalent normalization of serum calcium levels. It is not clear if this is due to differences in the technique itself or is related to the patients' perceptions of having had a 'less invasive' surgical procedure.

Indications for and results of video-assisted parathyroidectomy by lateral approach in patients with primary hyperparathyroidism

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Background: During the past few years different minimally invasive techniques of parathyroidectomy have been described. A retrospective study was performed to evaluate the indications and results of video-assisted parathyroidectomy by lateral approach (VAPLA) in the management of patients with primary hyperparathyroidism (PHPT).

Methods: From 1997 to 2000, 293 patients with PHPT were studied. VAPLA was proposed in patients with sporadic PHPT in whom a single adenoma was localized by ultrasonography and/or sestamibi scanning. VAPLA was performed by a lateral approach on the anterior border of the sternocleidomastoid muscle (SCM). Quick parathyroid hormone assay (QPTH) was used during surgery.

Results: Of the 293 patients, 127 (43·3 per cent) were not eligible for VAPLA because of ipsilateral previous neck surgery (28 patients), associated nodular goitre (59), suspicion of multiglandular disease (15), no preoperative localization (17) and other miscellaneous causes (eight). VAPLA was performed in 166 patients (56·7 per cent). Conversion to conventional parathyroidectomy was required in 26 patients (15·7 per cent) for the following reasons· adenoma not found (six patients), atypical or large adenomas (four; one carcinoma), false negative on QPTH (two), false positive on imaging studies (six) and multiglandular disease not suspected before operation but correctly predicted by QPTH (eight). Morbidity comprised two haematomas in the SCM, one definitive recurrent nerve palsy and four capsular effractions of large adenomas. All of the 167 patients were normocalcaemic at follow-up ranging from 3 to 33 months.

Conclusion: VAPLA is safe and effective. It can be included in the spectrum of different techniques for parathyroidectomy but should be reserved for patients with a small single adenoma, without ipsilateral previous neck surgery and associated thyroid disease.

Prospective randomized study of scan-directed unilateral exploration *versus* bilateral cervical exploration for parathyroid adenoma

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Background: Focused unilateral cervical exploration for primary hyperparathyroidism (PHPT) due to presumed solitary adenoma is now practised with increasing frequency. However, there remains the concern that this approach may result in additional, enlarged parathyroid glands being left *in situ* on the contralateral, unexplored side of the neck.

Methods: All patients diagnosed with PHPT and who had a positive preoperative sestamibi–technetium scintigram (one residual focus of activity following subtraction) were randomized to unilateral or bilateral cervical exploration.

Results: Between 1 April 1998 and 30 November 2000, 52 patients were studied. Of these, 26 had unilateral exploration and 26 bilateral operation. During the same period 40 individuals underwent elective bilateral exploration for PHPT. Following operation none of the 52 study patients demonstrated persistent hypercalcaemia. However, two patients randomized to bilateral exploration were each found to have a second enlarged parathyroid on the contralateral side of the neck.

Conclusion: Preliminary results suggest that scan-directed unilateral cervical exploration represents a satisfactory surgical strategy for most patients with presumed solitary parathyroid adenoma. The study is ongoing.

Total parathyroidectomy without autotransplantation for treatment of secondary hyperparathyroidism in uraemic patients

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Background: The surgical procedure of choice for secondary hyperparathyroidism or uraemia is still debated. Total parathyroidectomy without tissue preservation (tPTX) requires long-term treatment with calcium and vitamin D, and may result in metabolic (low turnover) bone disease. A prospective evaluation of the clinical impact of these theoretical disadvantages was conducted and the results of tPTX were analysed.

Methods: Patients submitted to tPTX during the 10-year period 1990–1999 were studied. Outcome measures were symptom reduction of bone pain, pruritus and muscle weakness by visual analogue scale (VAS); biohumoral data (calcium, phosphate, alkaline phosphatase (ALP) and intact parathyroid hormone (iPTH)); and skeletal radiography. Oral doses of calcium and calcitriol were monitored.

Results: Forty-six patients underwent tPTX (24 women; mean age 49·3 (range 26–79) years). Forty patients were on haemodialysis and six on conservative therapy, 65 per cent were excluded from transplantation lists. Forty-four patients had four glands removed and two only three glands. Complications consisted of acute symptomatic hypocalcaemia in ten patients and non-specific complications in three. No laryngeal nerve palsies occurred. Forty-three subjects were available for follow-up. After a mean of 5·0 years, 39 were cured, two had persistent disease and two had relapsed. Five patients have died (late mortality) and seven underwent successful transplantation. Symptom reduction was experienced by 81 per cent of subjects with bone pain (VAS 3·8 of 10), 66 per cent with pruritus (VAS 2·2 of 10) and 70 per cent with weakness (VAS 1·6 of 10). Serum levels of iPTH, calcium and ALP returned to the normal range: mean(s.d.) iPTH from 1084·5(505·4) to 38·9(55·8) pg ml^{-1}, calcium from 10·3(1·1) to 9·4(0·9) mg dl^{-1}, and ALP from 670·2(626·1) to 176·0(106·6) units l^{-1}. The comparative evaluation of bone radiographs showed an improvement in all patients ($n = 30$). The doses of oral calcium and calcitriol were similar to those administered before operation.

Conclusion: Clinical symptoms or radiographic signs of metabolic bone disease are not observed after tPTX, even at long-term follow-up. Mean doses of oral calcium and calcitriol are the same as those used routinely in many uraemic patients and are well tolerated. All serum variables tend to normalize and in some patients iPTH levels remain very low. Given the excellent results, tPTX should be considered a reliable alternative in selected patients.

Safety of elective short-stay thyroid and parathyroid surgery

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Background: This paper reviews the results and complications arising from a policy of 'short stay' for all elective thyroid and parathyroid procedures performed by one surgeon.

Methods: Short-stay surgery was defined as discharge on day 1 after operation for all thyroid lobectomies and patients with primary hyperparathyroidism, and on day 2 for total thyroidectomy. All data were collected prospectively.

Results: Over an 18-month period 171 patients were treated, including 32 for parathyroid disease (mean age 58 years; 25 women) and 139 for thyroid disease (mean age 44 years; 116 women). Procedures include 31 parathyroidectomies (one failure), 83 lobectomies, 43 total thyroidectomies, six subtotal thyroidectomies, five isthmusectomies and two Sistrunk operations. On day 1 after lobectomy, median corrected calcium was 2·27 (range 2·03–2·53) mmol l^{-1}. The calcium level was 2·08 (range 1·73–2·37) and 2·18 (range 1·87–2·37) mmol l^{-1} on days 1 and 2 after total thyroidectomy. Delayed discharge by 1 day occurred after four of 32 parathyroid operations and five of 89 lobectomies. After total thyroidectomy discharge was delayed by 1 day in three of 43 patients and 2 days in six patients. Symptomatic hypocalcaemia was the main cause of delay in seven patients who required oral Calcichew. No patient received intravenous calcium. At 3 months'

follow-up two patients were on long-term calcium replacement. Complications included two cases of postoperative haemorrhage (both in recovery) and one recurrent laryngeal nerve injury.
Conclusion: For the majority of patients (99 per cent undergoing thyroid lobectomy or parathyroid surgery and 80 per cent undergoing total thyroidectomy) a short hospital stay of 1 or 2 postoperative nights is all that is required to ensure a safe and efficient use of hospital resources, and surgeon and patient time.

Who performs thyroid surgery – a review of current otolaryngological practice

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Background: Thyroid surgery has traditionally been a general surgical practice, but recently more otolaryngologists have been offering a thyroid service, particularly in the management of thyroid cancer as part of the development of head and neck superspecialization. The authors have quantified thyroid surgery performed by the different specialties, and looked more closely at the practice of otolaryngologists to assess case workload and management of thyroid disease.
Methods: Data were obtained from the Department of Health for thyroid surgery in all specialties for the financial year 1998–1999 for the whole of the UK. Operations were coded by Office of Population, Censuses and Surveys codes and by consultant specialty. The data for otolaryngology were validated against a survey of members of the British Association of Otolaryngologists - Head and Neck Surgeons (BAO-HNS) asked about their practice for thyroid and parathyroid surgery. Use of investigations of a simple clinical case (solitary thyroid nodule) was compared with best practice.
Results: General surgeons still perform most thyroid surgery (84 per cent of all cases) but ear nose and throat (ENT) surgeons now perform significant numbers (14 per cent of all cases, which translates to 1499 cases per annum). The types of operation in the two groups are similar. One hundred and two BAO-HNS members were performing thyroid surgery with a mean case load of 13·6 benign and 5·5 malignant thyroids per year. Thirty-seven per cent of ENT surgeons see thyroid patients in multidisciplinary clinics. Investigations of a solitary nodule included fine-needle aspiration (98 per cent of respondents), thyroid function tests (97 per cent) and ultrasonography (90 per cent). Thyroid antibodies were measured by 51 per cent. Only 31 per cent routinely used scintigraphy. Preoperative and postoperative cord checks are currently performed by 98 and 82 per cent respectively.
Conclusion: ENT surgeons are doing significant amounts of thyroid surgery and the numbers appear to be increasing. Many of these patients appear to be seen in multidisciplinary clinics and the commonest investigations include fine-needle aspiration cytology, thyroid function tests and ultrasonography. The formation of multidisciplinary teams including general surgeons and otolaryngologists who are committed to subspecialization can only improve the training and treatment outcomes.

Role of key caspases and cytochrome c in thyrocyte apoptosis

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Background: Thyrocyte programmed cell death (apoptosis) is key to normal cell turnover. A dysfunction in thyrocyte apoptosis with decreased cell death may lead to neoplasm and a cell death excess to hypothyroidism. The apoptotic process is controlled by pro-apoptotic pressures (Fas/FasL, TNF/TNFR, etc.) and survival factors (Bcl-2 family). The dysregulation of thyrocyte apoptosis has been studied using Hashimoto's thyroiditis as a model. Caspase and cytochrome c expression and activation were evaluated under basal conditions and following stimulation by plasma from patients with and without autoimmune thyroid disease. The expression and modulation of the caspase cascade inhibitor Bcl-X was also measured.
Methods: Thyrocytes derived from the digestion of thyroids from patients with multinodular goitre, Graves' disease and Hashimoto's thyroiditis were evaluated for generalized caspase activity using the flow cytometric Caspatag™ assay (Intergen, Oxford, UK), and the caspases 3, 8, 9 and cytochrome c expression were assessed under basal conditions and following alteration of the culture environment using Western blot analysis. Caspase 8 was also evaluated with immunohistochemistry. Bcl-X expression was studied in thyroids from ten patients with multinodular goitre, ten with Graves' disease and four with Hashimoto's thyroiditis by immunofluorescence (and quantified with confocal microscopy) and by Western blot analysis.
Results: Active caspases were present in all thyrocytes but more markedly so in Hashimoto's thyrocytes. The constitutive expression of the components of the apoptotic cascade assessed appeared to be equal in all types of thyrocytes, except for caspase 9 which was overexpressed by Hashimoto's thyrocytes. The caspases and cytochrome c were upregulated equally by human plasma. Bcl-X was constitutively underexpressed in Hashimoto's thyroiditis and downregulated by proinflammatory cytokines.
Conclusion: Caspase 9 is overexpressed in Hashimoto's thyrocytes, which may be due to the underexpression of Bcl-X in the same cells, a feature that can be modulated by proinflammatory cytokines. It is envisaged that *in vivo* specific caspase inhibitors operate to prevent completion of the activated caspase cascade in normal cells but that this fails in Hashimoto's thyrocytes.

Value of early parathyroid hormone assay after total thyroidectomy

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Background: The purpose of this study was to evaluate the role of early postoperative parathyroid hormone (PTH) assay after total thyroidectomy to identify patients at high risk of developing hypocalcaemic symptoms and patients who need full medical therapy to avoid hypocalcaemia.

Methods: Twenty-six consecutive patients were evaluated. In all cases PTH (before operation, 2, 24 and 48 h after surgery, and at 7 days) and calcium levels (before operation, and 1, 2 and 7 days after surgery) were measured. Clinical evidence of hypocalcaemic syndrome and the need for full substitutive therapy (calcium and vitamin D) were assessed.

Results: Low PTH level at 2 h after surgery was statistically correlated to late hypocalcaemic symptoms ($P = 0{\cdot}007$) and to the need for increasing calcium and vitamin D therapy ($P = 0{\cdot}04$). At 24 h there was no correlation between PTH values and clinical features of hypocalcaemia. Decreased levels of PTH were predictive of hypocalcaemia on day 2 after operation ($P = 0{\cdot}006$) and full drug therapy was requested in 70 per cent of patients ($P = 0{\cdot}001$). At 48 h low PTH was strongly associated with hypocalcaemia in the postoperative period ($P = 0{\cdot}01$), to evidence of clinical symptoms ($P = 0{\cdot}01$) and the need for drug therapy ($P = 0{\cdot}0002$). Some 92 per cent of patients showed normal PTH levels by day 7.

Conclusion: PTH assay may be useful for predicting high-risk patients. PTH assay performed 48 h after surgery seems to be of greatest value. However, PTH levels in the perioperative period and 1 day after operation may select patients who should receive early drug therapy.

Video-assisted thyroid lobectomy by a gasless approach

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Background: Neck surgery is one of the newest and most interesting fields of application of minimally invasive surgery. Different techniques for video-assisted neck surgery have been described. A new technique, minimally invasive totally gasless video-assisted thyroid lobectomy, is presented.

Methods: Between March 1999 and December 2000, 632 patients with thyroid disease underwent a surgical procedure (thyroidectomy or thyroid lobectomy). Thirty-five patients underwent a minimally invasive video-assisted hemithyroidectomy, because of a single and small (less than 3 cm) thyroid nodule. The technique was completely gasless.

Surgical technique: The patient, under general anaesthesia, was placed in a supine position, with the neck in slight extension. A 15–20-mm horizontal skin incision was performed 1 cm above the sternal notch. After the insertion of a 3-mm 30° laparoscope through the skin incision, complete dissection of the lobe from the strap muscles was carried out using laparoscopic instruments, 2 mm in diameter, and conventional microinstruments. Use of a grasper allowed downward retraction of the gland with good exposure of the upper pole. This was clipped using a regular 3-mm clip applier and divided with 2-mm endoscopic scissors. The lobe was gently lifted up and the inferior laryngeal nerve was exposed as well as both parathyroid glands. The lobe and the isthmus were resected using ultrasonic scissors. No drain was placed.

Conclusion: The results of surgery, the low complication rate, the decrease in postoperative pain and the excellent cosmetic outcome suggest that this technique could be a valid alternative to conventional surgery in patients requiring a thyroid lobectomy.

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Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**) Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript:^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence.

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